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COVID-19

March 2, 2020 by Josh Farkas

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biology

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basics

- COVID-19 is a non-segmented, positive sense RNA virus.
- COVID-19 is part of the family of coronaviruses. This contains:
  - (i) Four coronaviruses which are *widely* distributed and usually cause the common cold (but *can* cause viral pneumonia in patients with comorbidities).
  - (ii) SARS and MERS – these caused epidemics with high mortality which are somewhat similar to COVID-19. COVID-19 is most closely related to SARS.
- It binds via the angiotensin-converting enzyme 2 (ACE2) receptor located on type II alveolar cells and intestinal epithelia (Hamming 2004 (https://www.ncbi.nlm.nih.gov/pubmed/15141377)).
  - This is the *same* receptor as used by SARS (hence the technical name for the COVID-19, "SARS-CoV-2").
  - When considering possible therapies, SARS (a.k.a. "SARS-CoV-1") is the most closely related virus to COVID-19.
- COVID-19 is mutating, which may complicate matters even further (figure below). Virulence and transmission will shift over times, in ways which we cannot predict. New evidence suggests that there are roughly two different groups of COVID-19. This explains why initial reports from Wuhan described a higher mortality than some more recent case series (Tang et al. 2020 (https://academic.oup.com/nsr/advance-article/doi/10.1093/nsr/nwaa036/5775463#.XmA64GbsBuI.twitter) ; Xu et al 2020 (https://www.bmj.com/content/368/bmj.m606)).
  - 👁 Image showing evolution of COVID-19 here (https://i0.wp.com/emcrit.org/wp-content/uploads/2020/03/covid88evo.jpg?resize=1536%2C1218&ssl=1) .
  - Ongoing phylogenetic mapping of new strains can be found here (https://nextstrain.org/ncov) .

nomenclature used in this chapter

- Technically, the *virus* is supposed to be called "SARS-CoV-2" and the *clinical illness* is called "COVID-19." This gets confusing, so for this chapter the term COVID-19 will be used to refer to both entities.
- The term "SARS" will be used to refer to the *original* SARS virus from 2003 (which has currently been renamed SARS-CoV-1).

pathophysiology

- (1) ARDS
  - The primary pathology is ARDS, characterized by diffuse alveolar damage (e.g. including hyaline membranes). Pneumocytes with viral cytopathic effect are seen, implying *direct* virus damage (rather than a purely hyper-inflammatory injury; Xu et al 2/17) (https://www.thelancet.com/action/showPdf?pii=S2213-2600%2820%2930076-X) .
- (2) Cytokine storm
  - Emerging evidence suggests that some patients may respond to COVID-19 with an exuberant "cytokine storm" reaction (with features of bacterial sepsis or hemophagocytic lymphohistiocytosis (https://emcrit.org/pulmcrit/sepsis-hlh-overlap-syndrome-shlhos/)).
  - Clinical markers of this may include elevations of C-reactive protein and ferritin, which appear to track with disease severity and mortality (Ruan 3/3/20 (https://link.springer.com/article/10.1007/s00134-020-05991-x)).

stages of illness ??

- There seem to be different stages of illness that patients may move through.
  - (#1) <u>Replicative stage</u> – Viral replication occurs over a period of several days. An innate immune response occurs, but this response fails to contain the virus. Relatively mild symptoms may occur due to direct viral cytopathic effect and innate immune responses.
  - (#2) <u>Adaptive immunity stage</u> – An adaptive immune response eventually kicks into gear. This leads to falling titers of virus. However, it may also increase levels of inflammatory cytokines and lead to tissue damage – causing clinical deterioration. There is a suggestion that this could lead to virus-induced hemophagocytic lymphohistiocytosis (HLH)(<u>Mehta et al.</u> (https://www.thelancet.com/lancet/article/S0140-6736(20)30628-0)). More discussion about this entity and possible therapy <u>here</u> (https://emcrit.org/ibcc/influenza/#virus-associated_hemophatocytic_syndrome_(VAHS)) .
- This progression may explain the clinical phenomenon wherein patients are relatively OK for several days, but then suddenly deteriorate when they enter the adaptive immunity stage (e.g. <u>Young et al. 3/3/2020</u> (https://jamanetwork.com/journals/jama/fullarticle/2762688)).
- This has potentially important clinical implications:
  - Initial clinical symptoms aren't necessarily predictive of future deterioration. Sophisticated strategies may be required to guide risk-stratification and disposition (see below section on <u>prognosis</u> (#prognosis)).
  - Anti-viral therapies might need to be deployed *early* to work optimally (during the replicative stage).
  - Immunosuppressive therapy (e.g. low-dose steroid) might be best initiated during the *adaptive* immune stage (with a goal of blunting this immunopathologic response slightly, in the sickest patients). *But this is purely speculative.*

transmission

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large droplet transmission

- COVID-19 transmission can occur via *large* droplet transmission (with a risk limited to ~6 feet from the patient)(<u>Carlos del Rio 2/28</u> (https://jamanetwork.com/journals/jama/fullarticle/2762510)).
- This is typical for respiratory viruses such as influenza.
- Transmission via large droplet transmission can be prevented by using a standard surgical-style mask.

airborne transmission ??

- It's controversial whether COVID19 can be transmitted via an airborne route (small particles which remain aloft in the air for longer periods of time). Airborne transmission would imply the need for N95 masks ("FFP2" in Europe), rather than surgical masks. This controversy is explored further in <u>Shiu et al 2019</u> (https://emcrit.org/wp-content/uploads/2020/03/tada2019.pdf) .
- Airborne precautions started being used with MERS and SARS out of an abundance of *caution* (rather than any clear evidence that coronaviruses are transmitted via an airborne route). This practice has often been carried down to COVID19.
- Guidelines *disagree* about whether to use airborne precautions:
  - The <u>Canadian Guidelines</u> (https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals.html) and <u>World Health Organization guidelines</u> (https://www-who-int.ezproxy.uvm.edu/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125) both recommend using only droplet precautions for routine care of COVID19 patients. However, both of these guidelines recommend airborne precautions for procedures which generate aerosols (e.g. intubation, noninvasive ventilation, CPR, bag-mask ventilation, and bronchoscopy).
  - The United States <u>CDC recommends</u> (https://www-cdc-gov.ezproxy.uvm.edu/coronavirus/2019-ncov/infection-control/control-recommendations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Finfection-control.html) using airborne precautions all the time when managing COVID19 patients.
- Using airborne precautions for all patients who are definitely or potentially infected with COVID19 will likely result in rapid depletion of N95 masks. This will leave healthcare providers unprotected when they actually need these masks for aerosol-generating procedures.
- In the context of a pandemic, the Canadian and WHO guidelines may be more sensible in countries with finite resources (i.e. most locales). However, infection control is ultimately local, so be sure to follow your hospital's guidance regarding this.

contact transmission ("fomite-to-face")

- This mode of transmission has a tendency to get overlooked, but it may be incredibly important. This is how it works:
  - (i) Someone with coronavirus coughs, emitting large droplets containing the virus. Droplets settle on surfaces in the room, creating a thin film of coronavirus. The virus may be shed in nasal secretions as well, which could be transmitted to the environment.
  - (ii) The virus persists on fomites in the environment. Human coronaviruses can survive on surfaces for up to about a *week* (<u>Kampf et al 2020</u> (https://www.ncbi.nlm.nih.gov/pubmed/32035997)). It's unknown how long COVID-19 can survive in the environment, but it might be even longer (some animal coronaviruses can survive for weeks!).
  - (iii) Someone else touches the contaminated the surface hours or days later, transferring the virus to their hands.
  - (iv) If the hands touch a mucous membrane (eyes, nose, or mouth), this may transmit the infection.
- Any effort to limit spread of the virus must block contact transmission. The above chain of events can be disrupted in a variety of ways:

- (a) Regular cleaning of environmental surfaces (e.g. using 70% ethanol or 0.5% sodium hypochlorite solutions; for details see Kampf et al 2020 (https://emcrit.org/wp-content/uploads/2020/02/10.1016@j.jhin_.2020.01.022-2.pdf) and CDC guidelines (https://www-cdc-gov.ezproxy.uvm.edu/coronavirus/2019-ncov/infection-control/control-recommendations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Finfection-control.html)).
  - (b) Hand hygiene (high concentration ethanol neutralizes the virus and is easy to perform, so this might be preferable if hands aren't visibly soiled) (Kampf 2017 (http://www.fha.org/files/JohnW/EM/Ethanol-hand-sanitizer-and-HAV.pdf)).
  - (c) Avoidance of touching your face. This is nearly impossible, as we unconsciously touch our faces constantly. The main benefit of wearing a surgical mask could be that the mask acts as a physical barrier to prevent touching the mouth or nose.
- *Any* medical equipment could become contaminated with COVID-19 and potentially transfer virus to providers (e.g. stethoscope earpieces and shoes). A recent study found *widespread* deposition of COVID-19 in one patient's room, but fortunately this seems to be removable by cleaning with sodium dichloroisocyanurate (Ong et al 2020 (https://jamanetwork.com/journals/jama/fullarticle/2762692)).

when can transmission occur?

- (#1) Asymptomatic transmission (in people with no or minimal symptoms) appears to be possible (Carlos del Rio 2/28 (https://jamanetwork.com/journals/jama/fullarticle/2762510)).
- (#2) Transmission appears to occur over roughly ~8 days following the initiation of illness.
  - Patients may continue to have positive pharyngeal PCR for weeks after convalescence (Lan 2/27 (https://jamanetwork.com/journals/jama/fullarticle/2762452)). However, virus culture methods are unable to recover viable virus after ~8 days of clinical illness (Wolfel 2020 (https://www.medrxiv.org/content/10.1101/2020.03.05.20030502v1.full.pdf)). This implies that prolonged PCR positivity probably *doesn't* correlate with clinical virus transmission. However, all subjects in Wolfel et al. (https://www.medrxiv.org/content/10.1101/2020.03.05.20030502v1.full.pdf) had mild illness, so it remains possible that prolonged transmission could occur in more severe cases.
  - CDC guidance (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html) is vague on how long patients with known COVID-19 should be isolated. It may be advisable to obtain two paired RT-PCR tests (one of the nasopharynx and one of the pharynx), with each pair collected >24 hours apart, prior to discontinuing precautions.

Rø

- Rø is the average number of people that an infected person transmits the virus to.
  - If Rø is <1, the epidemic will burn out.
  - If Rø = 1, then epidemic will continue at a steady pace.
  - If Rø >1, the epidemic will increase exponentially.
- Current estimates put Rø at ~2.5-2.9 (Peng PWH et al, 2/28 (https://bjanaesthesia.org/article/S0007-0912(20)30098-2/pdf)). This is a bit higher than seasonal influenza.
- Rø is a reflection of both the virus and *also* human behavior. Interventions such as social distancing and improved hygiene will *decrease* Rø.
  - Control of spread of COVID-19 in China proves that Rø is a *modifiable* number that can be reduced by effective public health interventions.
  - The Rø on board the Diamond Princess cruise ship was 15 – illustrating that cramped quarters with inadequate hygiene will *increase* Rø (Rocklov 2/28 (https://academic.oup.com/jtm/advance-article/doi/10.1093/jtm/taaa030/5766334)).

personal protective equipment (PPE)

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gear

- (1) Contact precautions (waterproof gown and gloves)
- (2) Some sort of mask (discussed above in the transmission (#transmission) section)
  - N95 mask or a powered, air-purifying respiratory ("PAPR")
  - Surgical mask for patients not undergoing aerosol-generating procedures (based on WHO & Canadian guidelines)
- (3) Goggles or eye shield
- *Note: The exact gear used is probably less important than using it correctly.*

applying and removing PPE (donning & doffing)

- Understanding how to put on (don) and remove (doff) personal protective equipment is *extremely important* (especially if contact transmission is a dominant mode of transmission).
- *Removing* soiled PPE is the most critical and difficult aspect.
- Applying and removing PPE should ideally be practiced *before* patients arrive (e.g. using simulation).
- The video below describes how to use PPE (you may skip the first 5 minutes).

NETEC: Personal Protective Equipment for COVID-19

some pearls about personal protective equipment

- Pay attention to the junction between gloves and gowns. The gown should be tucked into the gloves (leaving no gap in-between). Using gloves with extended cuffs facilitates this (similar to sterile surgical gloves). Gloves with long cuffs may facilitate removal of the gown and gloves as a *single unit* (see 12:30 in the above video if this doesn't make sense).
- When removing PPE, *always* start by *first* applying alcohol-based hand sanitizer to your gloves.
- After fully removing PPE, sanitize hands *and wrists* with alcohol-based hand sanitizer again.
- Create a step-wise protocol for PPE removal. Two examples are shown below, but this may very depending on your exact gear. Follow the steps slowly.
    - 👁 Checklist (https://i2.wp.com/emcrit.org/wp-content/uploads/2020/03/pperemovegood.jpg?w=1484&ssl=1) for removing PPE, using a tear-away gown here (this type of gown is preferred)
    - 👁 Checklist (https://i0.wp.com/emcrit.org/wp-content/uploads/2020/03/pperemove2.jpg?resize=1520%2C1536&ssl=1) for removing PPE, using a gown with fixed neck ties.
- Consider doffing with someone watching you (to ensure good technique). If this isn't possible, doffing in a mirror may be helpful.

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screening & selection for investigation

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key considerations include

- (1) Recent travel to affected areas.
    - Areas with community-based transmission are increasing *rapidly*.
    - The incubation time is up to 14 days, so travel within that window is relevant.
    - The importance of travel will decrease over time, as coronavirus starts being transmitted within the community.
- (2) Contact with anyone with known COVID-19 (defined as a prolonged period of time spent <6 feet apart).
- (3) As community acquisition emerges, broader testing will be needed. This will be based on a more *detailed* clinical evaluation, weighing:
    - i) How well patients meet the clinical features of Coronavirus (e.g. laboratory and imaging features explored further below).
    - ii) Presence or absence of alternative diagnoses (e.g. if patient tests positive for influenza, this would make it less likely that they *simultaneously* contracted influenza and coronavirus).

approach to isolation and testing

- Below is a general strategy aimed at rapid isolation of potentially infected patients, although it's already out of date for the following reasons:
    - (1) Travel risk has been updated by the CDC to include South Korea, Iran, Italy, and Japan (and at this point might also be appropriate to include some other areas in Europe).
    - (2) Many areas with community spread are starting to screen patients *without* defined epidemiological exposure.
- This is only intended as a general rubric. Be sure to follow your institutional protocols. Close communication with infection control, infectious disease specialists, and the local health department is essential.
    - Note that *some patients may present with gastrointestinal symptoms*. Unfortunately, most diagnostic algorithms will fail to detect and isolate these patients.

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signs and symptoms

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signs & symptoms

- COVID-19 may cause constitutional symptoms, upper respiratory symptoms, lower respiratory symptoms, and, less commonly, gastrointestinal symptoms. Most patients will present with constitutional symptoms and lower respiratory symptoms (e.g. fever and cough).
  - 👁 Table (https://i1.wp.com/emcrit.org/wp-content/uploads/2020/03/sxjpg.jpg?resize=1536%2C934&ssl=1) of symptoms described by various studies.
- Fever:
  - The frequency of fever is *variable* between studies (ranging from 43% to 98% as shown in the table above). This may relate to exact methodology used in various studies, different levels of illness severity between various cohorts, or different strains of the virus present in various locations. Additionally, some studies defined fever as a temperature >37.3 C (Zhou et al. 3/9/20 (https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930566-3)).
  - Regardless of the exact numbers – *absence of a fever does not exclude COVID-19.*
- Gastrointestinal presentations: up to 10% of patients can present initially with gastrointestinal symptoms (e.g. diarrhea, nausea), which *precede* the development of fever and dyspnea (Wang et al. 2/7/20 (https://jamanetwork.com/journals/jama/fullarticle/2761044)).
- "Silent hypoxemia" – some patients may develop hypoxemia and respiratory failure without dyspnea (especially elderly)(Xie et al. 2020 (https://link.springer.com/content/pdf/10.1007/s00134-020-05979-7.pdf)).
- Physical examination is generally nonspecific. About 2% of patients may have pharyngitis or tonsil enlargement (Guan et al 2/28 (https://www.nejm.org/doi/pdf/10.1056/NEJMoa2002032?articleTools=true)).

typical disease course

- *Incubation* is a median of ~4 days (interquartile range of 2-7 days), with a range up to 14 days (Carlos del Rio 2/28 (https://jamanetwork.com/journals/jama/fullarticle/2762510)).
- Typical evolution of severe disease (based on analysis of multiple studies by Arnold Forest (https://www.youtube.com/watch?v=zFrghcp5pbY&feature=youtu.be))
  - Dyspnea ~ 6 days post exposure.
  - Admission after ~8 days post exposure.
  - ICU admission/intubation after ~10 days post exposure. However, this timing may be *variable* (some patients are stable for several days after admission, but subsequently deteriorate rapidly).

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labs

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👁 Table (https://i0.wp.com/emcrit.org/wp-content/uploads/2020/03/labsjpg.jpg?resize=1536%2C1115&ssl=1) of general laboratory findings described in several studies.

complete blood count

- WBC count tends to be normal.
- Lymphopenia is common, seen in ~80% of patients (Guan et al 2/28 (https://www.nejm.org/doi/pdf/10.1056/NEJMoa2002032?articleTools=true) , Yang et al 2/21 (https://www.thelancet.com/action/showPdf?pii=S2213-2600%2820%2930079-5)).
- Mild thrombocytopenia is common (but platelets are rarely <100). Lower platelet count is a poor prognostic sign (Ruan et al 3/3 (https://link.springer.com/article/10.1007/s00134-020-05991-x)).

coagulation studies

- Coagulation labs are generally fairly normal upon admission, although elevated D-dimer is commonly seen (table above).
- Disseminated intravascular coagulation may evolve over time, correlating with poor prognosis (figure below)(Tang et al. 2020 (https://www.ncbi.nlm.nih.gov/pubmed/32073213)).
  - 👁 Image of DIC labs in survivors versus non-survivors over time here (https://i1.wp.com/emcrit.org/wp-content/uploads/2020/03/dicevo.jpg?resize=636%2C600&ssl=1) .

inflammatory markers

- Procalcitonin
  - COVID-19 does *not* appear to increase the procalcitonin. For example, the largest series found that procalcitonin levels were <0.5 in 95% of patients (Guan et al 2/28 (https://www.nejm.org/doi/pdf/10.1056/NEJMoa2002032?articleTools=true)).
  - Elevated procalcitonin may suggest an alternative diagnosis (e.g. pure bacterial pneumonia). For patients who have been admitted with COVID-19, procalcitonin elevation may suggest a superimposed bacterial infection.
- C-reactive protein (CRP)
  - COVID-19 increases CRP. This seems to track with disease severity and prognosis. In a patient with severe respiratory failure and a *normal* CRP, consider non-COVID etiologies (such as heart failure).
  - Young et al. 3/3 (https://jamanetwork.com/journals/jama/fullarticle/2762688) found low CRP levels in patients not requiring oxygen (mean 11 mg/L, interquartile range 1-20 mg/L) compared to patients who became hypoxemic (mean 66 mg/L, interquartile range 48-98 mg/L).
  - Ruan et al 3/3 (https://link.springer.com/article/10.1007/s00134-020-05991-x) found CRP levels to track with mortality risk (surviving patients had a median CRP of ~40 mg/L with an interquartile range of ~10-60 mg/L, whereas patients who died had a median of 125 mg/L with an interquartile range of ~60-160

mg/L)(figure below in the section on prognosis (#prognosis)).

evaluation for competing diagnoses

- PCR for influenza and other respiratory viruses (e.g. RSV) may be helpful. Detection of other respiratory viruses doesn't prove that the patient *isn't* co-infected with COVID-19 (~5% of patients may be co-infected with both COVID-19 and another virus)(Wang et al. (https://www.medrxiv.org/content/10.1101/2020.02.12.20022327v2)). However, an alternative explanation for the patient's symptoms will reduce the index of suspicion for COVID-19 substantially.
- Conventional viral panels available in some hospitals will test for "coronavirus."
    - This test does *not* work for COVID-19!
    - This PCR test for "coronavirus" is designed to evaluate for four coronaviruses which usually cause mild illness.
    - Ironically, a positive conventional test for "coronavirus" actually makes it *less likely* that the patient has COVID-19.
- Blood cultures should be performed as per usual indications.

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specific testing for COVID-19

Currently in the United States, all testing is done by state reference labs. Specimen collection and testing should be coordinated with the department of health.

specimens

- (1) Nasopharyngeal swab should be sent.
- (2) If intubated, tracheal aspirate should be performed.
- (3) Bronchoalveolar lavage or induced sputum are other options for a patient who isn't intubated. However, obtaining these specimens may pose substantial risk of transmission.
    - It's dubious whether these tests are beneficial if done for the sole purpose of evaluating for coronavirus (see the section below on bronchoscopy (#bronchoscopy)).

limitations in determining the performance of RT-PCR

- There are several major limitations, which make it hard to precisely quantify how RT-PCR performs.
- (1) RT-PCR performed on nasal swabs depends on obtaining a sufficiently deep specimen. Poor technique will cause the PCR assay to under-perform.
- (2) COVID-19 isn't a binary disease, but rather there is a *spectrum* of illness. Sicker patients with higher viral burden may be more likely to have a positive assay. Likewise, sampling *early* in the disease course may reveal a lower sensitivity than sampling later on.
- (3) Most current studies lack a "gold standard" for COVID-19 diagnosis. For example, in patients with positive CT scan and negative RT-PCR, it's murky whether these patients truly have COVID-19 (is this a false-positive CT scan, or a false-negative RT-PCR?).
    - (Convalescent serologies might eventually solve this problem, but this data isn't available currently.)

specificity

- *Specificity* seems to be high (although contamination *can* cause false-positive results).

sensitivity may not be terrific

- Sensitivity compared to CT scans
    - In a case series diagnosed on the basis of clinical criteria and CT scans, the sensitivity of RT-PCR was only ~70% (Kanne 2/28).
    - Sensitivity varies depending on assumptions made about patients with conflicting data (e.g. between 66-80%)(Ai et al. (https://pubs.rsna.org/doi/pdf/10.1148/radiol.2020200642)).
    - 👁 Image of analysis of Ai et al to determine sensitivity & specificity of PCR here (https://i1.wp.com/emcrit.org/wp-content/uploads/2020/03/perfctpcr.jpg?resize=732%2C600&ssl=1) .
- Among patients with suspected COVID-19 and a negative initial PCR, repeat PCR was positive in 15/64 patients (23%). This suggests a PCR sensitivity of <80%. Conversion from negative to positive PCR seemed to take a period of days, with CT scan often showing evidence of disease well *before* PCR positivity (Ai et al. (https://pubs.rsna.org/doi/pdf/10.1148/radiol.2020200642)).
- Bottom line?
    - PCR seems to have a sensitivity somewhere on the order of ~75%.
    - A single negative RT-PCR *doesn't* exclude COVID-19 (*especially* if obtained from a nasopharyngeal source or if taken relatively early in the disease course).
    - If the RT-PCR is negative but suspicion for COVID-19 remains, then ongoing isolation and re-sampling several days later should be considered.

CXR & CT scan

## general description of imaging findings on chest x-ray and CT scan

- The typical finding is patchy ground glass opacities, which tend to be predominantly peripheral and basal (Shi et al 2/24 (https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930086-4)). The number of involved lung segments increases with more severe disease. Over time, patchy ground glass opacities may coalesce into more dense consolidation.
- Infiltrates may be subtle on chest X-ray (example above from Silverstein et al (https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930370-6)).
  - 👁 Image of example chest X-ray here (https://i1.wp.com/emcrit.org/wp-content/uploads/2020/02/covidcxr.jpg?resize=750%2C380&ssl=1) .
  - 👁 Image of example CT scans here (https://i0.wp.com/emcrit.org/wp-content/uploads/2020/02/covct.jpg?resize=768%2C809&ssl=1) .
- Findings which *aren't* commonly seen, and might argue for an alternative or superimposed diagnosis:
  - Pleural effusion is uncommon (seen in only ~5%).
  - COVID-19 doesn't appear to cause masses, cavitation, or lymphadenopathy.

sensitivity and time delay

- Limitations in the data
  - Data from different studies conflict to a certain extent. This probably reflects varying levels of exposure intensity and illness severity (cohorts with higher exposure intensity and disease severity will be more likely to have radiologic changes).
- Sensitivity of CT scanning?
  - Sensitivity among patients with positive RT-PCR is high. Exact numbers vary, likely reflecting variability in how scans are interpreted (there currently doesn't seem to be any precise definition of what constitutes a "positive" CT scan).
    - Sensitivity of 86% (840/975) in Guan et al. (https://www.nejm.org/doi/pdf/10.1056/NEJMoa2002032?articleTools=true)
    - Sensitivity of 97% (580/601) in Ai et al (https://pubs.rsna.org/doi/pdf/10.1148/radiol.2020200642) .
  - Among patients with *constitutional* symptoms only (but *not* respiratory symptoms), CT scan may be less sensitive (e.g., perhaps ~50%)(Kanne 2/27 (https://pubs.rsna.org/doi/10.1148/radiol.2020200527)).
- CT scan abnormalities might emerge *before symptoms?*
  - Shi et al. (https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930086-4) performed CT scanning in 15 healthcare workers who were exposed to COVID-19 *before* they became symptomatic.
  - Ground glass opacification on CT scan was seen in 14/15 patients! 9/15 patients had peripheral lung involvement (some bilateral, some unilateral).
  - Emergence of CT abnormality *before* symptoms could be consistent with the existence of an asymptomatic carrier state (discussed above).
- Chest X-ray
  - Sensitivity of chest X-ray is lower than CT scan for subtle opacities. In Guan et al. (https://www.nejm.org/doi/pdf/10.1056/NEJMoa2002032?articleTools=true) , the sensitivity of chest x-ray was 59%, compared to 86% for CT scan.

Martin Schranz
@martinpschranz

Quality CT/XR images on proven COVID-19 provided by Prof. Dr. Filippo Cademartiri, Chairman of Radiology , Marche - Italy.
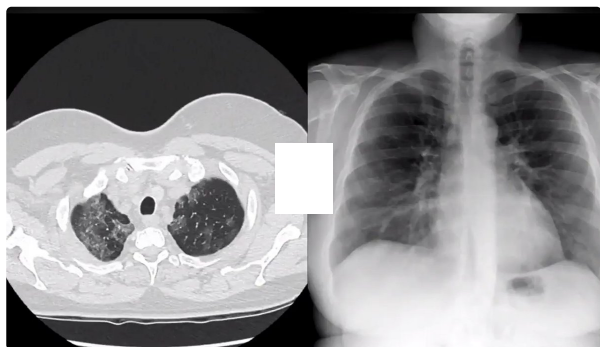
603   4:45 PM - Mar 5, 2020

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lung ultrasonography

technique

- In order to achieve sensitivity, a thorough lung examination is needed (taking a "lawnmower" approach, attempting to visualize as much lung tissue as possible).
- A linear probe may be preferable for obtaining high-resolution images of the pleural line (to make the distinction between a smooth, normal pleural line versus a thickened and irregular pleural line).
- COVID-19 typically creates patchy abnormalities on CT scan. These will be missed unless ultrasonography is performed *overlying* the abnormal lung tissue.

findings

- The findings on lung ultrasonography appear to correlate very well with the findings on chest CT scan.
- With increasing disease severity, the following evolution may be seen (Peng 2020 (https://link.springer.com/content/pdf/10.1007/s00134-020-05996-6.pdf))
  - (A) Least severe: *Mild* ground-glass opacity on CT scan correlates to scattered B-lines.
  - (B) More confluent ground-glass opacity on CT scan correlates to *coalescent* B-lines ("waterfall sign").
  - (C) With more severe disease, small peripheral *consolidations* are seen on CT scan and ultrasound.
  - (D) In the most severe form, the volume of consolidated lung increases.
  - 👁 Image of these patterns here (https://i1.wp.com/emcrit.org/wp-content/uploads/2020/03/USprogression.jpg?resize=712%2C600&ssl=1) .
- Other features:
  - Peripheral lung abnormalities can cause disruption and thickening of the pleural line.
  - Areas of normal lung (with an A-line pattern) can be seen early in disease, or during recovery.
  - Tiny pleural effusions may be seen, but substantial pleural effusions are uncommon (Peng 2020 (https://link.springer.com/content/pdf/10.1007/s00134-020-05996-6.pdf)).
  - As with CT scans, abnormalities are most common in the posterior & inferior lungs.
- For excellent examples of the correlation between CT scan and lung ultrasonography see Huang et al (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3544750) .

performance

- Sensitivity of lung ultrasonography isn't clearly defined.
  - Sensitivity will depend on several factors (most notably disease severity, presence of obesity, and thoroughness of scanning).
  - My guess is that a thorough ultrasound exam might have a sensitivity somewhere between CT scanning and chest X-ray (e.g., perhaps sensitivity ~75%?)(Huang et al. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3544750)). There isn't solid data yet, but it's probably reasonable to extrapolate from our experiences regarding other types of pneumonia.
- Specificity is extremely low. A patchy B-line or consolidation pattern can be seen in any pneumonia or interstitial lung disease. Thus, clinical correlation is necessary (e.g., evaluation of prior chest imaging studies to see if chronic abnormalities are present).
  - Note that supine, *hospitalized patients* may have B-lines and consolidation in a posterior and inferior distribution due to *atelectasis*. Thus, the lung ultrasonography may have greatest sensitivity and specificity among ambulatory patients.

**Adam Thomas** @adamdavidthomas · Mar 8, 2020
Replying to @adamdavidthomas
The right lung shows areas of "A" profile and occasional patches of B- Lines.

Adam Thomas
@adamdavidthomas

Given our base right of COVID-19 is increasing daily, you suspect said infection, isolate the patient and order further imaging to exclude other aspects of the Ddx for Dyspnea & Cough. Non contrast CT Chest shows diffuse ground glass opacities
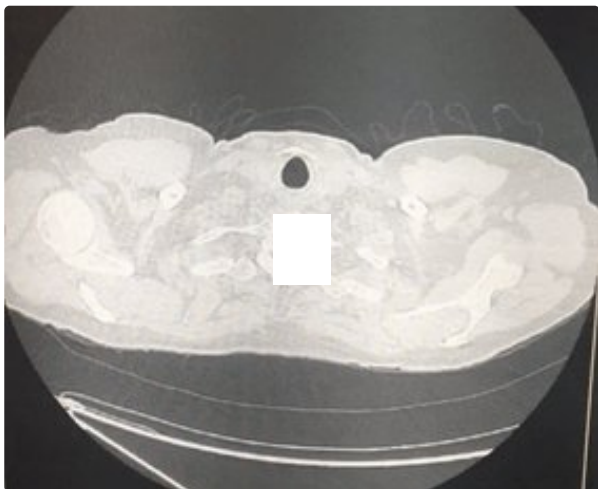
12 3:31 AM - Mar 8, 2020

See Adam Thomas's other Tweets

general approach to imaging

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all imaging modalities are nonspecific

- All of the above techniques (CXR, CT, sonography) are nonspecific. Patchy ground-glass opacities may be caused by a *broad* range of disease processes (e.g. viral and bacterial pneumonias). For example, right now in the United States, someone with patchy ground-glass opacities on CT scan would be *much* more likely to have a garden variety viral pneumonia (e.g. influenza or RSV) rather than COVID-19.
- Imaging *cannot* differentiate between COVID-19 and other forms of pneumonia.
- Imaging *could* help differentiate between COVID-19 and non-pulmonary disorders (e.g. sinusitis, non-pulmonary viral illness).
- Ultimately, the imaging is only one bit of information which must be integrated into clinical context.

possible approach to imaging in COVID-19

- Below is one possible strategy to use for patients presenting with respiratory symptoms and possible COVID-19.
- The temptation to get a CT scan in all of these patients should be resisted. In most cases, a CT scan will probably add little to chest X-ray and lung ultrasonography (in terms of *actionable* data which affects patient management).
- From a critical care perspective, CT scanning will likely add little to the management of these patients (*all* of whom will have diffuse infiltrates).
- ⊙ Schema (https://i1.wp.com/emcrit.org/wp-content/uploads/2020/03/imagcovid.jpg?resize=750%2C372&ssl=1) for imaging patients with respiratory symptoms and suspected COVID-19.

additional information:

- RSNA focus page on coronavirus (https://pubs.rsna.org/2019-nCoV#images) (contains fantastic slide show that provides an appreciation of possible imaging findings in a few minutes)

bronchoscopy

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- Risks of bronchoscopy:
  - May cause some deterioration in clinical condition (due to instillation of saline and sedation).
  - Enormous risk of transmission to providers.
  - Considerable resource allocation (requires N95 respirators, physicians, respiratory therapists) – all resources which will be in slim supply during an epidemic.
- Benefits of bronchoscopy:

- Benefit of diagnosing COVID-19 is dubious at this point (given that treatment is primarily supportive).
- Bottom line on bronchoscopy?
  - Bronchoscopy might be considered in situations where it would otherwise be performed (e.g. patient with immunosuppression with concerns for Pneumocystis pneumonia or fungal pneumonia).
  - Bronchoscopy should *not* be done for the purpose of ruling COVID-19 in or out (as this entails risk with no definite benefits)(Bouadma et al. (https://link.springer.com/content/pdf/10.1007/s00134-020-05967-x.pdf)).

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diagnostic approach for admitted patients

👁 One possible diagnostic approach (https://i0.wp.com/emcrit.org/wp-content/uploads/2020/03/covidalgoo.jpg?w=2148&ssl=1) to the ill patient admitted to hospital with suspected COVID-19.

- This approach is based on the availability of a PCR assay for COVID with a reasonably short turn-around time. This currently isn't a reality in most locations in the United States. Hopefully it will be soon.
- Requiring a negative influenza PCR *before* testing for COVID isn't desirable, because ~5% of patients may be co-infected (Wang et al. (https://www.medrxiv.org/content/10.1101/2020.02.12.20022327v2)). Thus, a positive influenza PCR *cannot* exclude COVID. The rate of double-positivity may increase over time, as the prevalence of COVID in the community increases.
- The largest challenge may be determining who needs to be ruled out for COVID (i.e. who needs to be entered into this algorithm in the first place). Currently there is no simple answer for this – clinical judgement is required.
  - Ruling out too *many* patients will result in excessive consumption of masks in patients who don't have COVID. Additionally, placing patients under COVID precautions may impair their care (e.g., isolation may serve as a barrier to obtaining scans or family visitation).
  - Ruling out too *few* patients may result in nosocomial transmission of COVID.

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key principle: supportive care for viral pneumonia

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general principle: avoid COVID-19 exceptionalism

- We know how to treat severe viral pneumonia and ARDS. We've been doing this for years.
- There is not yet any compelling evidence that the fundamentals of treating COVID-19 are substantially different from treating other forms of viral pneumonia (e.g. influenza).
- The essential strategy of treatment for COVID-19 is supportive care, which should be performed as it would be done for any patient with severe viral pneumonia. For example, if you were to simply treat the patient as if they had influenza (minus the oseltamivir), you would be doing an excellent job.
- Below are some *minor adjustments* on the care that we provide, which might optimize things a bit for treating COVID-19. However, overall the treatment is fundamentally the same as for treating any viral pneumonia.

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general template for intubated ICU patient

The following template is intended as a general guide, which will need to be adapted to various different contexts. For an overview of supportive care in the ICU, see *this chapter (https://emcrit.org/ibcc/guide/) .*

daily examination: focus on

- Vent
  - Ventilator settings & synchrony with ventilator.
  - Confirm ETT depth at the upper teeth (ensure no migration of the tube).
  - *Tighten* connections between ETT, connecting tubing, and ventilator (to prevent accidental disconnection).
- Neurologic status.
- Cardiac and lung ultrasonography (may perform Q48 or Q72hr if stable).

daily labs

- Electrolytes, Creatinine, Magnesium, Phosphate
- CBC *with differential*
- DIC labs (INR, PTT, fibrinogen, D-dimer)

- HLH labs (C-reactive protein, Ferritin, LDH)
- Troponin (to surveil for development of *myocarditis*, not acute coronary syndrome)
- Triglycerides every 72 hours for patients on propofol (surveillance for propofol infusion syndrome)
- (*Avoid* ABG/VBG as much as possible)

cardiovascular

- Avoid fluid boluses (more on this here (https://emcrit.org/pulmcrit/coronavirus/) and here (https://emcrit.org/pulmcrit/bolus/)) & avoid maintenance fluid.
- Target even or negative fluid balance.
- Low-dose vasopressor use as necessary to support MAP.

pulmonary

- Lung-protective ventilation (consider early APRV).
- Permissive hypercapnia (e.g. target pH over perhaps ~7.15 if hemodynamics allow).
  - Consider trending etCO2 and minute ventilation *instead* of obtaining serial ABG/VBG measurements (to avoid excess phlebotomy).
- For acidosis, make sure that metabolic acid-base status is optimized *before* adjusting the ventilator.
  - Generally target a serum bicarbonate in the high-normal range (e.g. ~28 mEq/L).
  - ICU patients often have non-anion-gap metabolic acidosis (https://emcrit.org/ibcc/nagma/) (NAGMA). Treatment of NAGMA with bicarbonate (https://emcrit.org/ibcc/fluid/#hypertonic_&_isotonic_bicarbonate) may be the safest way to address a low pH (rather than increasing the intensity of mechanical ventilation and thereby threatening the lung).

gastrointestinal

- Enteral nutrition.
- Stress ulcer prophylaxis.

renal

- Avoid nephrotoxins (including NSAIDs).
- Diuresis as necessary to achieve even fluid balance (if tolerated by hemodynamics).

infectious diseases

- Initially most patients will be on empiric antibiotics for bacterial pneumonia (e.g. azithromycin plus ceftriaxone).
- Anti-viral therapy if available (e.g. remdesivir).
- Follow microbiologic studies.

heme

- DVT prophylaxis (continue unless platelets extremely low, as COVID-19 may cause a pro-coagulable form of DIC despite low platelet count).

endocrine

- Follow glucose levels periodically.
- Insulin as needed to avoid severe hyperglycemia.

neurology

- Acetaminophen 1 gram enterally q6hr scheduled (for antipyretic and analgesic effects).
- Opioid bolus PRN pain (e.g. fentanyl 50 mcg IV q30 min PRN breakthrough pain).
- Low-dose propofol as a titratable sedative (e.g. ideally 0-40 mcg/kg/min).
- Melatonin 5 mg QHS for sleep.
- Consider adjunctive atypical antipsychotic QHS to encourage sleep and provide some basal sedation (e.g. 5-10 mg olanzapine per tube, QHS)
- For ongoing pain, could add a pain-dose ketamine infusion (0.1-0.3 mg/kg/hr)(more on this here (https://emcrit.org/pulmcrit/analgesic-ladder/)).

lines & tubes

- (1) Orogastric tube or small-bore post-pyloric feeding tube.
- (2) Central line
  - Low threshold to place a quad-lumen central line with meticulous sterility.
  - Best site may be left internal jugular vein (save the right internal jugular for dialysis or ECMO).
- (3) Arterial line

- Avoid if possible, as this may tend to encourage frequent ABG/VBG draws (which are unlikely to materially improve care and will cause anemia).

background on antiviral therapy

caveats on anti-viral therapy

- No anti-viral therapy has been proven to work for COVID-19 in humans. Multiple RCTs are ongoing; hopefully they will bring us further information soon.
  - *Whenever possible, patients should be enrolled in RCTs.*
- Information is provided below about some of the more popular agents which are being used by some practitioners.
  - Inclusion in this chapter is *not* a recommendation to use one or more of these medications. This information is simply provided as a background to help us understand these therapies.
  - A focus is placed on lopinavir/ritonavir and chloroquine since these agents are currently available.
  - Practitioners are encouraged to review available evidence and reach their own conclusions regarding whether to use these medications.
  - If you have experience or new evidence or opinions on anti-viral therapy, please share it on the COVID-19 discussion page here (https://emcrit.org/pulmcrit/covid19/) .

single vs. multi-drug regimens ??

- Another unknown is whether a *single* drug could work, or whether a combination of multiple anti-viral agents is needed.
- Analogous to HIV, it's possible that two or three anti-virals working in synergy might be needed. Combinations of agents could increase *toxicity* however (especially cardiotoxicity).

indications for antiviral therapy: who & when ??

- When ??
  - Retrospective data from SARS suggests that earlier treatment (e.g. within 1-2 days of admission) may be more effective than reserving therapy until severe organ failures occur (Chan 2003 (https://www.hkmj.org/abstracts/v9n6/399.htm)). This is consistent with data from influenza that suggests a finite treatment window occurring relatively early in the disease course.
- Who ??
  - The vast majority of patients will do fine without any therapy, so in most cases there's no need for antiviral therapy.
  - However, *waiting* until patients are severely ill before initiating therapy could cause us to miss an early treatment window, during which the disease course is more modifiable.
  - Predictors of adverse outcome might be useful in predicting who will do poorly and thus who might benefit most from early anti-viral therapy? (see section below on prognosis (#prognosis)).

remdesivir

- Remdesivir might be an excellent antiviral, based on a study involving *in vitro* and animal data with MERS (e.g. Sheahan 2020 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6954302/pdf/41467_2019_Article_13940.pdf)).
- Unfortunately, remdesivir is not commercially available. Remdesivir was used on the basis of "compassionate use" for one of the first patients with COVID-19 in the United States (Holshue 2020 (https://www.nejm.org/doi/full/10.1056/NEJMoa2001191)).
- Remdesivir is being used in one trial (https://clinicaltrials.gov/ct2/show/NCT04280705) in the United States being sponsored by NIAID. Enrollment in this trial is the most desirable approach to antiviral therapy (if feasible).

lopinavir/ritonavir (KALETRA)

general description

- This is a combination of antiviral agents used in treatment of HIV (including post-exposure prophylaxis following needle-stick injury).
- Compared to remdesivir, lopinavir/ritonavir has the advantage that it's widely available and has an established toxicity profile (it does have known side-effects and drug interactions, but these are generally tolerable).
- Lopinavir/ritonavir appears to work synergistically with ribavirin. Available human data on SARS and MERS have *combined* these three agents together. It's possible that a cocktail of all three drugs is required for efficacy (potentially explaining failures of any of these agents in isolation). A recent very small study on lopinavir/ritonavir alone wasn't particularly impressive, suggesting that triple therapy with lopinavir/ritonavir/ribavirin might be necessary (Young 3/3/20 (https://jamanetwork.com/journals/jama/fullarticle/2762688)).

mechanism of action

- Lopinavir and ritonavir are protease inhibitors, which block viral replication.
- Lopinavir seems to be the agent which actually acts on the virus. Ritonavir is a CYP3A inhibitor which functions primarily to reduce metabolism of lopinavir, thereby boosting lopinavir levels.

in vitro data

- Lopinavir showed *in vitro* antiviral activity against SARS at concentration of 4 ug/ml. However, when combined with ribavirin, lopinavir appears considerably more effective (with an inhibitory concentration of 1 ug/mL (Chu et al. 2004 (https://thorax.bmj.com/content/59/3/252.long)).
- For reference, the peak and trough serum concentrations of lopinavir are 10 and 5.5 ug/ml (Chu et al. 2004 (https://thorax.bmj.com/content/59/3/252.long)).

animal data

- Lopinavir/ritonavir was effective against MERS-CoV in a primate animal model (Chan 2015 (https://www.ncbi.nlm.nih.gov/pubmed/26198719)).

human data

- Chu et al. 2004 (https://thorax.bmj.com/content/59/3/252.long) : Open-label before/after study on SARS.
  - 41 patients treated with lopinavir/ritonavir plus ribavirin were compared to 111 historical control patients treated with ribavirin alone. Baseline imbalances did exist between groups (patients treated with lopinavir/ritonavir had lower initial lactate dehydrogenase (LDH) levels – so they weren't as sick).
  - Poor clinical outcomes (ARDS or death) were lower in treatment group (2.4% vs. 29%). These differences persisted in multivariable models, which attempted to correct for baseline imbalances between the groups.
  - Use of lopinavir/ritonavir use correlated with a dramatic reduction in viral load.
  - All patients received concomitant ribavirin. The dose was 4 grams oral loading dose followed by 1.2 grams PO q8hr (or 8 mg/kg IV q8hr) for 14 days.
- Chan et al. 2003 (https://www.hkmj.org/abstracts/v9n6/399.htm) : Retrospective matched multi-center cohort study on SARS
  - 75 patients treated with lopinavir/ritonavir were compared with controls (matched on the basis of sex, age, comorbidities, lactate dehydrogenase level, and use of pulse-dose steroid).
  - Up-front treatment with lopinavir/ritonavir combined with ribavirin correlated with reduced mortality (2.3% versus 16%). However, rescue therapy with lopinavir/ritonavir (often *without* concomitant ribavirin) didn't seem to make any difference. The ribavirin dose was 2.4 grams loading dose, followed by 1.2 grams PO q8hr (or 8 mg/kg IV q8hr) for 10-14 days.
  - 👁 Image of viral load over time in Chan et al. here (https://i2.wp.com/emcrit.org/wp-content/uploads/2020/03/loprit.jpg?resize=768%2C1172&ssl=1) .
- Park et al. 2019 (https://www.ncbi.nlm.nih.gov/pubmed/30240813) : Retrospective cohort study on post-exposure prophylaxis against MERS
  - This is a retrospective cohort study involving 22 patients with high-risk exposure to a single MERS patient (table below). As a control group, four hospitals with outbreaks of MERS were selected.
  - Post-exposure prophylaxis consisted of a combination of lopinavir/ritonavir (400 mg / 100 mg BID for 11-13 days) plus ribavirin (2000 mg loading dose, then 1200 mg q8hr for four days, then 600 mg q8hr for 6-8 days).
  - MERS infections didn't occur in anyone treated with post-exposure prophylaxis. However, the manner in which the control group was selected (retrospectively selecting hospitals with MERS outbreaks) likely biased the study in favor of showing a benefit of post-exposure prophylaxis.
  - Post-exposure therapy was generally well tolerated, although most patients reported some side-effects (most commonly nausea, diarrhea, stomatitis, or fever). Laboratory evaluation shows frequent occurrence of anemia (45%), leukopenia (40%), and hyperbilirubinemia (100%).
  - 👁 Image of patient characteristics in Park et al. here (https://i2.wp.com/emcrit.org/wp-content/uploads/2020/03/merscov.jpg?resize=750%2C377&ssl=1) .
- Young et al. 3/3/2020 (https://jamanetwork.com/journals/jama/fullarticle/2762688)
  - Cohort study describing 16 COVID-19 patients in Singapore. Among six patients with hypoxemia, five were treated with lopinavir/ritonavir (200 mg/100 mg BID, which is half of the usual dose of lopinavir).
  - Among the five patients, two patients deteriorated and had persistent nasopharyngeal virus carriage.
  - Possible reasons for these underwhelming results might include: statistical underpowering, low dose of lopinavir/ritonavir, lack of synergistic ribavirin, and/or late initiation of therapy. For further discussion see PulmCrit blog on this study here (https://emcrit.org/pulmcrit/lopinavir/) .
- Other evidence of lower quality:
  - Lopinavir/ritonavir has been used to treat one patient with COVID-19 (Kim 2020 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7025910/pdf/jkms-35-e79.pdf)).
  - Lopinavir/ritonavir was reported to be effective in some case reports of MERS (Momattin 2019 (https://www.ncbi.nlm.nih.gov/pubmed/31252170)).
- Lopinavir/ritonavir is currently under investigation within multiple RCTs in China (but none in the United States).

dosing

- (1) Lopinavir/Ritonavir (Monograph (https://reference.medscape.com/drug/kaletra-lopinavir-ritonavir-342629) from MedScape)
  - Standard dose (and dose used against coronaviruses) is 400 mg / 100 mg PO BID.
  - Generally no adjustment is made in renal dysfunction.

- Crushing and administering tablets via a gastric tube may decrease absorption by ~50%. Increased doses might be considered in this situation (Best et al. 2011 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3205189/)).
- (2) Ribavirin (Monograph (https://reference.medscape.com/drug/rebetol-ribasphere-ribavirin-342625) from MedScape)
  - Unknown whether synergistic ribavirin is useful.
  - The best validated regimen is probably Chu et al. 2004 (https://thorax.bmj.com/content/59/3/252.long) : 4 grams oral loading dose followed by 1.2 grams PO q8hr (or 8 mg/kg IV q8hr) for 14 days.

contraindications/cautions regarding Lopinavir/Ritonavir:

- Serious adverse effects may include:
  - Hypersensitivity reaction, angioedema
  - Stevens-Johnson syndrome / Toxic epidermal necrolysis / Erythema multiforme
  - QT prolongation & Torsade de Pointes
  - AV block, PR prolongation
  - Hyperglycemia, hypertriglyceridemia
  - Renal failure
  - Anemia, leukopenia, neutropenia
  - Pancreatitis
  - Hepatotoxicity
- Common adverse reactions:
  - Nausea/vomiting, diarrhea
  - Insomnia, anxiety
- Contraindicated in:
  - Cardiac disease (ischemic heart disease, cardiomyopathy, structural heart disease, QT prolongation)
  - Liver disease
- Monitoring: Transaminase levels
- Overall tolerability?
  - In Chu et al. 2004 (https://thorax.bmj.com/content/59/3/252.long) , 41 patients with SARS tolerated lopinavir/ritonavir reasonably well (one patient needed to discontinue due to doubling of transaminase levels).
  - In Chan 2003 (https://www.hkmj.org/abstracts/v9n6/399.htm) , 75 patients with SARS were treated with lopinavir/ritonavir without reports of severe adverse effects.

additional information:

- PulmCrit blog 3/4 (https://emcrit.org/pulmcrit/lopinavir/) discussing the Young study and double vs. triple therapy.
- Further information on this is available in a recent review by Yao TT et al. (https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25729)

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chloroquine

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general description

- Chloroquine is generally used for treatment of malaria and amebiasis. It has anti-viral activity in vitro, but no established track record in treatment of viral disease.
- The toxicity profile seems to be acceptable (e.g. its widely used as malaria prophylaxis — albeit at a much lower dose than is currently being considered for COVID-19).

mechanism of action

- Chloroquine appears to work via multiple mechanisms, including:
  - Interference with with the cellular receptor ACE2 (potentially making it particularly effective against SARS and COVID-19).
  - Impairment of acidification of endosomes, which interferes with virus trafficking within cells.
- Chloroquine also has immunosuppressive activities. It's unknown whether such immunosuppressive action could be *beneficial* or *harmful* (analogous to steroid therapy).

in vitro data

- *In vitro* data using cell lines shows that chloroquine can inhibit COVID-19 with an 50% inhibitory concentration of 1 uM, implying that therapeutic levels could be achieved in humans (Wang 2020 (https://www.ncbi.nlm.nih.gov/pubmed/32020029)). The 50% inhibitory concentration of chloroquine for SARS is closer to 9 uM, suggesting that chloroquine could be more effective against COVID-19 than SARS (Al-Bari 2017 (https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1002/prp2.293)).

animal data

- Chloroquine failed to work in mice infected with SARS (Bernard 2006 (https://www.ncbi.nlm.nih.gov/pubmed/17176632)).

human data

- Emerging reports from China suggests that chloroquine has been studied with favorable results, but data is currently not available (Gao 2020 (https://www.jstage.jst.go.jp/article/bst/advpub/0/advpub_2020.01047/_pdf/-char/en)). An expert consensus group in China is recommending a treatment regimen of 500 mg PO twice daily for patients without contraindications (Zhi 2020 (https://www.ncbi.nlm.nih.gov/pubmed/32075365)). Hopefully, clinical data with chloroquine will be published shortly.

dosing (Monograph (https://reference.medscape.com/drug/aralen-chloroquine-phosphate-chloroquine-342687) from MedScape)

- 500 mg chloroquine *phosphate* contains 300 mg of chlorquine itself (a.k.a. chloroquine base).
- 500 mg PO twice daily for 10 days is the regimen recommended by a group in China for patients without contraindications (Zhi 2020 (https://www.ncbi.nlm.nih.gov/pubmed/32075365)).
- May require dose adjustment in renal or hepatic dysfunction.

contraindications/cautions

- Serious adverse effects may include:
  - QT prolongation & Torsades de Pointes
  - Reduction in seizure threshold
  - Anaphylaxis or anaphylactoid reaction
  - Neuromuscular impairment
  - Neuropsychiatric disorders (potential to increase delirium)
  - Pancytopenia, neutropenia, thrombocytopenia, aplastic anemia
  - Hepatitis
- Common adverse reactions:
  - Nausea/vomiting, diarrhea, abdominal pain
  - Visual disturbance, headache
  - Extrapyramidal symptoms
- Monitoring: Serial complete blood count, QT interval
- Contraindicated in: Porphyria, G6PD deficiency, epilepsy, heart failure, recent myocardial infarction.

comments

- Mixed messages from China regarding how widely this is being used or recommended.
  - Many articles don't mention chloroquine at all.
  - A few articles strongly recommend this (Zhi 2020 (https://www.ncbi.nlm.nih.gov/pubmed/32075365) , Gao 2020 (https://www.jstage.jst.go.jp/article/bst/advpub/0/advpub_2020.01047/_pdf/-char/en))
- Chikungunya Virus Caveat: Chloroquine was effective for chikungunya virus *in vitro,* but subsequently failed to work in primate model (in fact, immunosuppressive effects of chloroquine actually *increased* viral levels)(Roques et al 2018 (https://www.ncbi.nlm.nih.gov/pubmed/29772762)). This underscores the fact that *in vitro* effects on cell lines may not necessarily translate into beneficial clinical effects (especially given complex immunomodulatory effects of chloroquine).
- Hopefully additional data will be forthcoming shortly.

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oseltamivir & other neuraminidase inhibitors

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- Neuraminidase inhibitors *don't* seem to work against COVID-19 (Tan et al 2004 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3323075/pdf/03-0458.pdf)).
- Initial empiric therapy with neuraminidase inhibitors could be reasonable during influenza season in critically ill patients, if there is concern that the patient might have influenza pneumonia.
  - Currently, in many locations, patients presenting with viral pneumonia are much more likely to have influenza than COVID-19.

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steroid

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steroid

- Steroid should *not* generally be used. Steroid hasn't demonstrated benefit in prior SARS or MERS epidemics. Steroid may increase viral shedding (Lee 2004 (https://www.sciencedirect.com/science/article/pii/S1386653204001957?via%3Dihub)).
- Nearly all articles recommend against the use of steroid. However, steroid may be used if there is *another* clear-cut indication for steroid (e.g. coronavirus plus asthma exacerbation, refractory septic shock).
  - WHO guidelines summary the relevant evidence regarding steroid; for further information read them here (https://t.co/dI0uTXTE0r?amp=1) (see bottom of page 4).

ascorbic acid ??

- Ascorbic acid did appear to improve mortality in the multi-center CITRIS-ALI trial (https://jamanetwork.com/journals/jama/article-abstract/2752063) . However, interpretation of this trial remains hopelessly contentious due to nearly unsolvable issues with survival-ship bias (discussed here (https://emcrit.org/pulmcrit/pulmcrit-citris-ali-can-a-secondary-endpoint-stage-a-coup-detat/)).
- Extremely limited evidence suggests that ascorbic acid could be beneficial in animal models of coronavirus (Atherton 1978 (https://www.ncbi.nlm.nih.gov/pubmed/205194)).
- Administration of a moderate dose of IV vitamin C could be considered (e.g. 1.5 grams IV q6 ascorbic acid plus 200 mg thiamine IV q12). This dose seems to be safe. However, *there is no high-quality evidence to support ascorbic acid in viral pneumonia.*

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tocilizumab

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basics

- Tocilizumab is a recombinant humanized monoclonal antibody which binds to the interleukin-6 (IL-6) receptor and blocks it from functioning.
- Tocilizumab is most commonly used to treat rheumatoid arthritis. It may also be used to treat cytokine release syndrome following CAR-T therapy.
- Mechanistically, tocilizumab would be expected to benefit patients with COVID-19 who develop a cytokine storm (which involves elevated levels of IL-6, a major pro-inflammatory cytokine).

evidentiary support

- No high-level evidence is currently available.
- Tocilizumab been used in Italy (podcast discussions regarding this here (https://podcasts.apple.com/ca/podcast/italian-covid19-experience/id1502496721?i=1000468384785) and here (https://jamanetwork.com/journals/jama/pages/conversations-with-dr-bauchner)).
- Case series from China (Xu et al.) (http://www.chinaxiv.org/abs/202003.00026)
  - 21 hypoxemic patients were treated with tociliumab 400 mg as an intravenous infusion (most patients received a single dose, but 3 patients received two doses).
  - Patients appeared to improve clinically, with rapid reduction in inflammatory markers. No adverse effects were noted.

comment

- Further evidence is needed. Hopefully this will be coming soon (tocilizumab may be one of the most promising agents under investigation).
- This could be a reasonable treatment for a patient with worsening multi-organ failure and laboratory evidence of severe inflammation (e.g. marked CRP elevation).

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anti-bacterial therapy

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initial empiric antibiotics

- COVID-19 itself is not an indication for antibiotics.
- Initially, there may be concerns regarding the possibility of a superimposed bacterial pneumonia. When in doubt, it may be sensible to obtain bacterial cultures and procalcitonin, prior to initiation of empiric antibiotic therapy. Based on culture and procalcitonin results, antibiotics might be discontinued in <48 hours if there isn't evidence of a bacterial infection (this is exactly the same as management of influenza pneumonia).

delayed bacterial superinfection

- Bacterial pneumonia can emerge during the hospital course (especially ventilator-associated pneumonia in patients who are intubated).
  - Among patients who died from COVID-19, one series found that 11/68 (16%) had secondary infections (Ruan 3/3/20 (https://link.springer.com/content/pdf/10.1007/s00134-020-05991-x.pdf)).
- This may be investigated and treated similarly to other ventilator-associated pneumonias, or hospital-acquired pneumonias.

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cardiovascular

avoid fluid resuscitation

- Patients *rarely* are shocked on admission (even among critically ill patients, admission blood pressure is generally normal and lactate elevations are mild-moderate)(Yang et al 2/21 (https://www.thelancet.com/action/showPdf?pii=S2213-2600%2820%2930079-5)).
  - Overall, the rate of reported "sepsis" is generally low (<5%). The virus doesn't seem to generally cause a septic shock picture (but of course, patients may always suffer from superimposed bacterial septic shock).
- The cause of death from COVID-19 is nearly always ARDS – which may be *exacerbated* by fluid administration.
- Gentle fluid administration could be considered for patients with evidence of hypoperfusion and a history suggestive of total body hypovolemia (e.g. prolonged nausea/vomiting and diarrhea).
- More discussion on fluid therapy for COVID-19 here (https://emcrit.org/pulmcrit/coronavirus/) .

troponin elevation

- Elevated troponin is common (especially high sensitivity troponin). This is a strong predictor of mortality (as is generally true for troponin elevation among critically ill patients).
- Troponin elevation generally doesn't represent a type-I (plaque rupture) myocardial infarction. As such, these elevations require no specific therapy.
- The value of measuring and cycling troponin is dubious. Evaluation should probably focus on EKG findings, because EKG findings of coronary occlusion would much greater implications for clinical management (true coronary occlusion is probably rare, but this can occur in any patient under physiologic stress). More on the evaluation of troponin in critical illness here (https://emcrit.org/ibcc/troponin/) .

cardiomyopathy

- Fulminant cardiomyopathy can occur. This may be a *late* feature, which can occur even after patients are recovering from respiratory failure.
- Cardiogenic shock appears to be an important cause of death, contributing to ~7-33% of deaths (Ruan 3/3/20 (https://link.springer.com/article/10.1007/s00134-020-05991-x)).
- It's unclear whether this represents a viral cardiomyopathy (virus *can* be recovered from myocardial tissue), stress cardiomyopathy, or cardiac dysfunction due to cytokine storm (i.e., a feature of virus-induced hemophagocytic lymphohistiocytosis).

additional information:

- Zheng YY et al. COVID-19 and the cardiovascular system (https://www.nature.com/articles/s41569-020-0360-5.pdf) . Nature Reviews, 3/5/20.
- The Coronavirus Conundrum (http://www.nephjc.com/news/covidace2) , Hypertension Edition (NephJC blog, by Matthew Sparks and Swapnil Hiremath et al.)
- Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Fang et al, Lancet 3/11/20 (https://www.thelancet.com/action/showPdf?pii=S2213-2600%2820%2930116-8) .

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high flow nasal cannula

safety of HFNC

- There is widespread concern that using HFNC could increase the risk of viral transmission. To my knowledge, however there is no solid evidence to support this fear.
- WHO guidelines on COVID-19 (https://t.co/dI0uTXTE0r?amp=1) state that "Recent publications suggest that newer HFNC and NIV systems with good interface fitting do not create widespread dispersion of exhaled air and therefore should be associated with low risk of airborne transmission."
- Reasons that HFNC might *not* increase viral transmission are:
  - HFNC supplies gas at a rate of ~40-60 liters/minute, whereas a normal cough achieves flow rates of ~400 liters/minute (Mellies 2014 (https://www.atsjournals.org/doi/full/10.1513/AnnalsATS.201406-264OC)). Therefore, it's doubtful that a patient on HFNC is more contagious than a patient on standard nasal cannula who is coughing.
  - HFNC typically requires less maintenance than invasive mechanical ventilation. For example, a patient who is on HFNC watching television may be less likely to spread the virus compared to an intubated patient whose ventilator is alarming every 15 minutes, requiring active suctioning and multiple providers in the room.
  - The intubation procedure places healthcare workers at enormous risk of acquiring the virus, so intubation with a goal of reducing transmission is probably counterproductive (see figure above from Tran 2012 (https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0035797&type=printable)).
    - 👁 Image of risk factors for nosocomial SARS transmission from Tran et al. here (https://i0.wp.com/emcrit.org/wp-content/uploads/2020/03/metahfnc.jpg?resize=768%2C962&ssl=1) .
  - Existing evidence does not support the concept that HFNC increases pathogen dispersal substantially (although the evidence is extremely sparse). This includes a small study of patients with bacterial pneumonia (Leung 2018 (https://www.journalofhospitalinfection.com/article/S0195-6701(18)30542-5/pdf)) and an

abstract regarding particulate dispersal by volunteers (Roberts 2015 (https://emcrit.org/wp-content/uploads/2020/03/roberts2015.pdf)).

- One possible *compromise* might be to use HFNC with a moderate rate of flow (e.g. 15-30 liters/minute, rather than 40-60 liters/minute). Since 15-30 liters/minute flow is close to a baseline minute ventilation for a sick respiratory failure patient, adding this level of flow is unlikely to affect matters substantially.

role of HFNC in COVID

- HFNC is generally a rational front-line approach to noninvasive support in patients with ARDS (based partially on the FLORALI trial (https://emcrit.org/pulmcrit/pneumonia-bipap-secretions-and-hfnc-new-lessons-from-florali/)).
- One case series from China suggested that HFNC was associated with higher rates of survival than either noninvasive or invasive ventilation (of course, this could reflect its use in less sick patients)(Yang et al, see table 2 (https://www.thelancet.com/action/showPdf?pii=S2213-2600%2820%2930079-5)).
- A management strategy for COVID-19 by a French group used HFNC preferentially, instead of BiPAP (Bouadma et al. (https://link.springer.com/content/pdf/10.1007/s00134-020-05967-x.pdf)).

when to transition from HFNC to intubation (when to determine that the patient has "failed" HFNC)

- COVID-19 may cause hypoxemia with relatively little respiratory distress ("silent hypoxemia"). For example, patients may be profoundly hypoxemic yet not be dyspneic – and such patients may "look" fine. Therefore, work of breathing cannot be relied upon to detect patients who are failing HFNC.
- There should probably be a lower threshold to intubate in COVID-19 than in most patients, for the following reasons:
  - Patients can develop worsening "silent" atelectasis and decline rather abruptly, without lots of symptoms.
  - Oxygenation techniques used to maintain saturation during intubation (e.g. mask ventilation) may increase virus aerosolization. Thus, "pure" rapid sequence intubation without bagging is preferred. This will be safer if the patient is starting out with more oxygenation reserve.
  - Intubation requires considerable preparation, so a semi-elective intubation is preferred to crash intubation.
- Exactly when to intubate is always a clinical decision. Progressively rising FiO2 requirements should be a signal to consider intubation (e.g. requirement of perhaps more than ~75% FiO2??).
- 👁 Schema (https://i1.wp.com/emcrit.org/wp-content/uploads/2020/03/respsup.jpg?resize=713%2C600&ssl=1) for escalating levels of respiratory support in patients with COVID-19.

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noninvasive ventilation (BiPAP)

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traditional BiPAP probably isn't useful for most patients

- Reasons to avoid BiPAP:
  - In a multicenter cohort of 302 patients with MERS coronavirus, 92% of patients treated with BiPAP failed this modality and required intubation (Alraddadi 2019 (https://www.ncbi.nlm.nih.gov/pubmed/30884185)).
  - In the FLORALI trial (https://emcrit.org/pulmcrit/pneumonia-bipap-secretions-and-hfnc-new-lessons-from-florali/) of ARDS patients (with mostly pneumonia of various etiologies), patients randomized to BiPAP did worse compared to patients randomized to HFNC.
- BiPAP could have a niche role in patients with combined syndromes (e.g. COPD plus COVID-19). For more on the selection of BiPAP vs. HFNC, see this chapter (https://emcrit.org/ibcc/support/) on noninvasive respiratory support.
- If BiPAP is used, a viral filter should be placed in-line with the exhalation tubing to reduce environmental contamination.

BiPAP using a helmet interface

- A helmet interface may have several advantages:
  - Could reduce environmental contamination (Cabrini 2020 (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30359-7/fulltext)).
  - Decreased risk of aspiration of emesis occurs.
  - Improved outcomes in one RCT of ARDS patients (Patel 2016 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4967560/)).
- Unfortunately, access to these devices is limited in the United States.

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intubation procedure
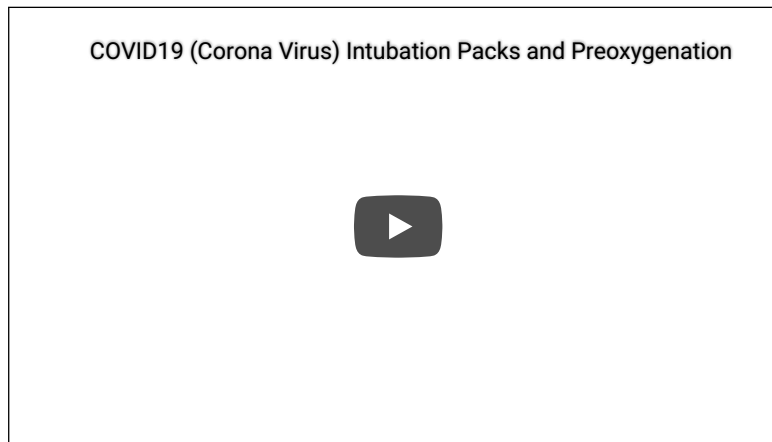
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- This represents a high risk for transmission to healthcare workers.
- Airborne precautions *are* indicated (e.g. N95/FFP2 masks or positive air-purifying respirators, along with full face shields and full contact precautions).

- Rapid sequence intubation with no bag-mask ventilation may avoid aerosolizing particles. However, during the apneic period, a bag-valve mask with a PEEP valve could be *passively* held on the patient's face to maintain positive pressure in the airway and thereby prevent de-recruitment.
- Use of videolaryngoscopy may avoid placing the operator's face close to the patient.
- Attach a *viral filter* to the bag-valve mask before the procedure, if possible. This should reduce the spread of viral particles out of the endotracheal tube following intubation (or during bag-mask ventilation if that is required)(Peng et al. 2/27 (https://bjanaesthesia.org/article/S0007-0912(20)30098-2/pdf)).
- Endotracheal tube confirmation with a stethoscope could pose a risk of transferring virus to the practitioner. It could be safer to advance the endotracheal tube to a pre-calculated depth calculated based on the patient's height (see MDCalc formula (https://www.mdcalc.com/endotracheal-tube-ett-depth-tidal-volume-calculator) here).
- 👁 Image (https://i1.wp.com/emcrit.org/wp-content/uploads/2020/03/covidtube.jpg?resize=768%2C1052&ssl=1) of intubation protocol for COVID-19.

more information

- Weingart: Some additional airway management thoughts (https://emcrit.org/emcrit/some-additional-covid-airway-management-thoughts/) (3/10); Intubation packs and preoxygenation for intubation (https://emcrit.org/emcrit/covid19-intubation-packs-and-preoxygenation-for-intubation/) (3/13 & embedded video 👇)

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invasive mechanical ventilation

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pathophysiology: COVID does not cause typical ARDS

- COVID doesn't appear to cause substantially reduced lung compliance (which is generally a hallmark finding of ARDS).
- The predominant problem might be one or more of the following:
    - (i) Atelectasis (alveolar collapse).
    - (ii) Drowning of the alveoli by fluid.
- If the predominant problem is atelectasis, then this will be relatively easy to manage. Any strategy to increase the mean airway pressure will treat atelectasis (e.g. APRV or conventional ARDSnet ventilation using a high-PEEP strategy).
- If *drowning* of the alveoli is a significant issue, this is a bit harder to manage. Proning may facilitate drainage of secretions. APRV may also be useful to facilitate airway clearance (rapid dumping breaths create expiratory airflow that can facilitate secretion clearance).

conventional ARDSnet ventilation

- Tidal volumes should be targeted to a lung-protective range (6 cc/kg ideal body weight).
    - MDCalc (https://www.mdcalc.com/endotracheal-tube-ett-depth-tidal-volume-calculator) can be used to calculate appropriate endotracheal tube depth & tidal volumes.
- High PEEPs should be utilized. An ARDSnet "high PEEP" table is shown below. This table doesn't need to be followed exactly, but it may be useful as a general guide.
    - 👁 Image of ARDSnet low-PEEP & high-PEEP tables here (https://i0.wp.com/emcrit.org/wp-content/uploads/2020/03/peep.gif?resize=350%2C361&ssl=1) .

airway pressure release ventilation (APRV)

- My opinion is that *early* APRV could be very useful for these patients (i.e. used as the initial ventilator mode, rather than a salvage mode). APRV may be well suited to the pathophysiology of COVID, because it provides a high mean airway pressure and facilitates secretion clearance.
- A practical guide to using APRV can be found here (https://emcrit.org/squirt/aprv/) . A reasonable starting place is generally:
    - P-high: 30-35 cm (higher if more profound hypoxemia)
    - P-low: zero
    - T-high: 5 seconds

- T-low: 0.5 seconds (titrate based on flow rates; consider reduction if tidal volume >8 cc/kg)
- Improvement in oxygenation seen with APRV often takes several hours as lung tissue gradually recruits.
- APRV initiation can cause hemodynamic shifts, so pay careful attention to blood pressure during initiation.
- True failure to respond to APRV within 12-24 hours (e.g. with PaO2/FiO2 <100-150) would be a strong argument to move towards prone ventilation (discussed here (https://emcrit.org/pulmcrit/pseudoards/)). However, when started early APRV may be more likely to succeed – thereby avoiding the need for proning.

permissive hypercapnia

- Regardless of the ventilator mode, permissive hypercapnia may be useful. The safe extent of permissive hypercapnia is unknown, but as long as hemodynamics are adequate a pH of >7.1 or >7.15 may be tolerable (hypercapnia is preferred over lung-injurious ventilation).
  - Slow administration of IV bicarbonate is an acceptable strategy to improve pH while simultaneously continuing lung-protective ventilation (discussed here (https://emcrit.org/pulmcrit/hypercapnia/)). Targeting a mildly elevated serum bicarbonate (e.g. 28-30 mEq/L) can facilitate safe ventilation with low tidal volumes (more on different forms of IV bicarbonate here (https://emcrit.org/ibcc/fluid/#hypertonic_&_isotonic_bicarbonate)).

proning

- Prior to consideration of proning, optimization on the ventilator for 12-24 is generally preferable (discussed here (https://emcrit.org/pulmcrit/pseudoards/)).
- For failure to respond to initial ventilator optimization (e.g. with persistent PaO2/FiO2 below 150 mm), prone ventilation should be considered.
- Reports from Italy describe proning as extremely effective.
  - This makes sense, because proning is expected to be effective for basilar lung recruitment and secretion clearance (which seem to be the primary problems with these patients).
  - The question is whether the same effect could be achieved more easily using APRV. Proning is very labor-intensive and will require consumption of lots of personal protective equipment (since multiple providers will need to the turn the patient repeatedly). If the same effect can be achieved with APRV, that could be an easier solution (especially at centers which lack extensive experience with proning).

additional information:

- Mechanical ventilation and coronavirus pneumonia (http://www.ventilab.org/2020/02/29/ventilazione-meccanica-e-polmonite-da-coronavirus/) (Giuseppe Natalini, ventilab blog, Google translation from Italian)

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disaster ventilation strategies

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awake prone ventilation

- This involves a non-intubated patient on nasal cannula who prone themselves by lying on their belly.
- There is relatively little evidence to support this. It is useful only for highly selected patients (reviewed here (https://emcrit.org/pulmcrit/proning-nonintubated/)).
- Awake-prone ventilation could be a useful option if the availability of mechanical ventilators is exhausted.
  - Typically awake prone ventilation is paired with high-flow nasal cannula, but it could also be used with a standard nasal cannula (e.g. running at ~6 L/min or a bit higher if tolerated).
  - Consider securing the nasal cannula to the patient's face using tape or tegaderm, to prevent dislodgment when the patient moves.

splitting ventilators

- In a dire emergency, one ventilator can be used to support several patients.
- Discussion and guideline for this here (https://emcrit.org/pulmcrit/split-ventilators/) .

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renal failure

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- Renal failure requiring dialysis is reported in a subset of patients admitted to ICU.
- The exact mechanism is unclear at this point, but some conjectures may be reached based on SARS (Chu et al. 2005 (https://www.kidney-international.org/article/S0085-2538(15)50506-1/pdf)).
  - SARS causes renal failure in ~7% of patients. The pathology shows acute tubular necrosis, which appears to be a reflection of generalized multi-organ failure. In some cases rhabdomyolysis may have contributed as well. Renal failure correlates with a poor overall prognosis (92% mortality with renal failure versus 9% without). In multivariable analysis, renal failure was the strongest predictor of mortality (more-so even than ARDS).

ECMO

- Patients with COVID-19 can be relatively young and suffering from single-organ failure due to a reversible etiology, so many would be excellent candidates for ECMO.
  - VV ECMO could be used for respiratory failure (although it's unclear how common true refractory hypoxemia is).
  - VA ECMO could be useful in patients with fulminant cardiomyopathy and cardiogenic shock
- Exact indications and timing are unclear.
- In an epidemic, ECMO capabilities would probably rapidly become saturated. Very thorny ethical issues could arise (e.g. how long of an ECMO run is one patient allowed to have before the withdrawal of life-sustaining therapy, in order to allow the circuit to be used for another patient).

going further

- [Infographics on ECMOed](https://ecmoed.blog/2020/03/11/covid-19-infographics/) (https://ecmoed.blog/2020/03/11/covid-19-infographics/) by M Velia Antonini

prognosis

general prognosis

- (1) It remains unclear what fraction of patients are hospitalized.
  - There may be lots of patients with mild illness who don't present to medical attention and aren't counted.
  - The vast majority of infected patients (e.g. >80%) *don't* get significantly ill and *don't* require hospitalization.
- (2) Among *hospitalized* patients ([Guan et al 2/28](https://www.nejm.org/doi/pdf/10.1056/NEJMoa2002032?articleTools=true) (https://www.nejm.org/doi/pdf/10.1056/NEJMoa2002032?articleTools=true))
  - ~10-20% of patients are admitted to ICU.
  - ~3-10% require intubation.
  - ~2-5% die.
- (3) Longer term outcomes: Prolonged ventilator dependency ?
  - Patients who survive the initial phases of the illness may still require prolonged ventilator support (possibly developing some radiographic elements of fibrosis)([Zhang 2020](https://link.springer.com/article/10.1007/s00134-020-05990-y) (https://link.springer.com/article/10.1007/s00134-020-05990-y)).
  - As the epidemic progresses, an issue which may arise is a large volume of patients unable to wean from mechanical ventilation.
- (*Caveat*: There are *numerous* sets of numbers published and they vary *a lot*. However, from the clinician's standpoint the precise numbers don't really matter.)

epidemiological risk factors

- Risk factors ([Zhou et al. 3/9/20](https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930566-3) (https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930566-3)).
  - Older age
  - Coronary artery disease
  - Hypertension
  - Diabetes
  - Chronic pulmonary disease
- The largest series of mortality data comes from the [Chinese CDC](http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51) (http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51) (table below). The *absolute* numbers may vary depending on whether some cases were missed, but the *relative* impact of various risk factors is probably accurate.
  - 👁 Image of mortality related to age and comorbidity [here](https://i1.wp.com/emcrit.org/wp-content/uploads/2020/02/mortdata.jpg?resize=768%2C1053&ssl=1) (https://i1.wp.com/emcrit.org/wp-content/uploads/2020/02/mortdata.jpg?resize=768%2C1053&ssl=1) .

laboratory risk stratification

- **Blood cell count abnormalities**
  - *Lymphopenia* and its trends over time (prolonged or worsening lymphopenia portends poor outcome)([Chu et al. 2004](https://thorax.bmj.com/content/59/3/252.long) (https://thorax.bmj.com/content/59/3/252.long))
  - [Neutrophil/lymphocyte ratio (NLR)](https://emcrit.org/pulmcrit/nlr/) (https://emcrit.org/pulmcrit/nlr/) appears to be a superior prognosticator when compared to either lymphopenia or C-reactive protein ([Liu et al. pre-print](https://www.medrxiv.org/content/10.1101/2020.02.10.20021584v1.full.pdf) (https://www.medrxiv.org/content/10.1101/2020.02.10.20021584v1.full.pdf)). As shown in the second figure below, neutrophil/lymphocyte ratios >3 could suggest a worse prognosis.
- Other predictors of poor outcome include markers of inflammation (**C-reactive protein** and **ferritin**), **lactate dehydrogenase**, and **D-dimer**. D-dimer elevation over 1 ug/L was the strongest independent predictor of mortality in [Zhou et al. 3/9/20](https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930566-3) (https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930566-3) .
- Troponin is a prognostic factor, but it may be challenging to compare values obtained across different laboratories.
- (References: [Ruan 3/3/20](https://link.springer.com/article/10.1007/s00134-020-05991-x) (https://link.springer.com/article/10.1007/s00134-020-05991-x) , [Xie et al. 2020](https://link.springer.com/article/10.1007/s00134-020-05979-7) (https://link.springer.com/article/10.1007/s00134-020-05979-7) , [Wang et al. 2/7/20.](https://jamanetwork.com/journals/jama/fullarticle/2761044) (https://jamanetwork.com/journals/jama/fullarticle/2761044) , [Zhou et al. 3/9/20](https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930566-3) (https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930566-3))
- 👁 Image of D-dimer, ferritin, LDH, and Lymphocyte trends over time in survivors & non-survivors [here](https://i2.wp.com/emcrit.org/wp-content/uploads/2020/03/zhoupx-scaled.jpg?resize=750%2C321&ssl=1) (https://i2.wp.com/emcrit.org/wp-content/uploads/2020/03/zhoupx-scaled.jpg?resize=750%2C321&ssl=1) .

- 👁 Image of C-reactive protein, troponin, and IL-6 in survivors vs. non-survivors here (https://i0.wp.com/emcrit.org/wp-content/uploads/2020/03/ruancovid.jpg?resize=639%2C600&ssl=1) .
- 👁 Image of WBC, lymphocytes, and D-dimer over time in survivors vs. non-survivors here (https://i0.wp.com/emcrit.org/wp-content/uploads/2020/03/wangjamapx.jpg?resize=768%2C934&ssl=1) .

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disposition

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avoidance of unnecessary emergency department or clinic visits

- Health systems should ideally be put in place to dissuade patients from presenting to the clinic or emergency department for testing to see if they have COVID-19 (e.g. if they have mild constitutional symptoms and don't otherwise require medical attention).
- Many centers have developed drive-thru testing, which avoids exposure of other patients in the emergency department. Outdoor testing also ensures ongoing circulation of fresh air.

home disposition

- The vast majority of patients with coronavirus will recover spontaneously, without requiring any medical attention (perhaps >80% of patients).
- Patients with mild symptoms can generally be discharged home, with instructions to isolate themselves. These decisions should be made in coordination with local health departments, who can assist in follow-up.
- Features favoring home discharge may include:
  - Ability to understand and comply with self-isolation (e.g. separate bedroom and bathroom).
  - Ability to call for assistance if they are deteriorating.
  - Having household members who aren't at increased risk of complications from COVID-19 (e.g. elderly, pregnant women, or people with significant medical comorbidities).
  - Lack of hypoxemia, marked chest infiltrates, or other features that would generally indicate admission.
- For more, see CDC interim guidance for disposition of patients with COVID-19 here (https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html) and here (https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-home-care.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fguidance-home-care.html) .

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podcast

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(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/apps.40518.14127333176902609.7be7b901-15fe-4c27-863c-7c0dbfc26c5c.5c278f58-912b-4af9-88f8-a65fff2da477.jpg)

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The Podcast Episode

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questions & discussion

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To keep this page small and fast, questions & discussion about this post can be found on another page *here* (https://emcrit.org/pulmcrit/COVID19/) .

- Delayed consideration of COVID19, leading to delayed initiation of precautions (e.g. in a patient presenting with gastrointestinal illness).
- Treatment of COVID19 based on Surviving Sepsis Guidelines (e.g. with 30 cc/kg fluid). This is wrong on so many levels (https://emcrit.org/pulmcrit/coronavirus/) , for example:
  - Broad application of 30 cc/kg fluid is often *detrimental* in septic shock.
  - COVID-19 patients don't actually present with septic shock anyways.
  - Large volume fluid is extremely dangerous in ARDS.
- Inadequate attention to contact precautions (e.g. hand hygiene and sterilization of surfaces).
- Admission of patients to hospital for COVID19 who could be safely managed as outpatients.
- Use of the emergency department as a COVID-19 screening area.
- Be careful of making *major* changes to usual treatment approaches for viral pneumonia, based on limited evidence. Ultimately the key here is simply high-quality supportive care for viral pneumonia.

Going further:

- Journal & Society homepages on COVID-19
  - CDC (https://www.cdc.gov/coronavirus/index.html)
  - JAMA (https://jamanetwork.com/journals/jama/pages/coronavirus-alert)
  - LANCET (https://www.thelancet.com/coronavirus)
  - NEJM (https://www.nejm.org/coronavirus)
  - BMJ (https://www.bmj.com/coronavirus)
  - ESICM (https://www.esicm.org/resources/coronavirus-public-health-emergency/)
  - AMA (https://www.ama-assn.org/topics/coronavirus-covid-19)
- FOAMed on COVID-19
  - WHO guidelines on fluid administration for COVID-19 are dangerous (https://emcrit.org/pulmcrit/coronavirus/) (PulmCrit)
  - EMCrit RACC on airway management (https://emcrit.org/emcrit/airway-covid-19/) in COVID-19 (Weingart & Brian Wright)
  - COVID-19 on RebelEM (https://rebelem.com/covid-19-the-novel-coronavirus-2019/) (Salim Rezaie)
  - COVID-19 on St. Emlyns (https://www.stemlynsblog.org/2019-novel-coronavirus-wuhan-at-st-emlyns/) (Ashley Liebig)
  - COVID-19 on Radiopaedia (https://radiopaedia.org/articles/covid-19?fbclid=IwAR2G1HjFlbP1aj3Inj_-HqG27NM3lx8TXE4VpTpTHUu0PYWRTJmHvIqbVAE) (Daniel Bell)
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