Seven Lessons Learned from COVID-19 - Physiology

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Learning objectives

1) Describe topics in pathophysiology like hypercoagulability and V/Q abnormalities that have been illustrated by the COVID-19 pandemic.

2) Describe topics in transmission and risk of contracting COVID-19.

3) Understand the historical place of the COVID-19 pandemic compared to other recent pandemics.
No conflicts of interest related to this subject matter
Seven Lessons Learned from COVID-19

- Physiology

1) Correcting V/Q ratios likely improves outcomes in COVID-19 illness
2) COVID-19 illness is primarily a disease of inflammation
3) In illnesses with a high survival rate like COVID-19, it is difficult to prove treatment efficacy
4) The accuracy of antibody tests is like fishing
5) Air currents let you get away with it
6) Vitamin D and COVID-19
7) Historically, viral pandemics proceed in waves
Miss America 2020
Some background

- My hodgepodge clinical and teaching practice
- McGehee service and COVID-only units
- COVID-19 facts of the day
- COVID-19 Essays from the Front
- History of COVID-19 project
- COVID-19 Life Stories
COVID-19 Essays from the Front

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Lesson 1: Correcting V/Q ratios likely improves outcomes in COVID-19 illness
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- When we are healthy, there is a near-perfect match between the air that makes its way to the alveoli and the blood that moves through the capillaries near the alveoli.
- Part of “getting in shape” entails better matching up ventilation with perfusion by matching up capillary blood flow and alveolar air flow.
- An important part of chronic lung diseases, like emphysema, is a further mismatch of ventilation and perfusion and the loss of lung efficiency.
Lesson 1: Correcting V/Q ratios likely improves outcomes in COVID-19 illness

- With pronation, ill patients are placed on their stomach for at least part of the day in an effort to better match up ventilation and perfusion.
- Intermittent Prone Positioning (IPP) for Acute Respiratory Distress Syndrome (ARDS) decreases mortality.
- Preliminary data shows that this technique can reduce the need for artificial ventilation in very ill patients.
- “Although awake prone positioning may be a promising therapy for patients with hypoxemic respiratory failure (including those with COVID-19), the supporting evidence is limited to case reports and cohort studies.”  
  (Weatherald, J Crit Care. 2021 Feb;61:63-70)
When the COVID-19 pandemic began, it was understandably presumed that smoking would be associated with worse outcomes.

Patients with inefficient ventilation, like those with asthma and COPD often suffer exacerbations of their conditions that are set off by viral infections, like influenza.

However, observation has shown that COVID-19 illness is not mainly a disease of ventilation. For example, multiple studies have shown that infected patients with asthma do not have greater rates of hospitalization or death.
Lesson 1: Correcting V/Q ratios likely improves outcomes in COVID-19 illness

- COVID-19 itself appears to be a disease of gas exchange, as COVID-19 pneumonia thickens the alveoli and impedes oxygen and carbon dioxide movement through a combination of virus killing normal cells and inflammation.

- COVID-19 may also increase blood clotting in very small alveolar blood vessels, again worsening gas exchange.

- A retrospective review of 7000 patients infected with COVID-19 found that persons with a significant smoking history (more than 30 pack-years) were about twice as likely to need hospitalization and about twice as likely to die compared to non-smokers who were infected with COVID-19. (Lowe, JAMA Internal Medicine, Jan 25 2021)
WE WILL RECOVER
Lesson 2: COVID-19 illness is primarily a disease of inflammation
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- With COVID-19 disease the immune response is important and sometimes puzzling.

- We know for example that patients with a suppressed immune system do worse with COVID-19. However, we also know that there is a period of the illness in some patients in which the immune response is inappropriately high.

- Part of the difficulty in identifying effective treatments for COVID-19 illness has been the fact that patients appear to have two distinct stages of illness.
Inflammation

Pain

Warn

Swelling

Redness

Harmful things enter the body
Lesson 2: COVID-19 illness is primarily a disease of inflammation

- In the first phase, viral growth is rampant, and decreasing the ability of the virus to replicate and infect new cells appears to be a helpful intervention.

- However, at some point, usually between 7 and 14 days after infection, inflammation—which is helpful early on to contain viral spread—may become excessive and damaging in and of itself.
Lesson 2: COVID-19 illness is primarily a disease of inflammation

- There are two phases of disease, a viral growth phase extending 7 to 14 days during which inflammation is helpful, and a later phase, fortunately not experienced by most, in which inflammation can become harmful and even deadly.

- How can we tell which patients will have a proper inflammatory reaction to knock out the virus and which patients will have an inappropriate inflammatory reaction, one that does more harm than good?
  - One way appears to be by measuring blood markers of inflammation, like C-reactive protein, D-dimer, and troponin.
Lesson 3: In illnesses with a high survival rate like COVID-19, it is difficult to prove treatment efficacy
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- Early on in the pandemic, little was known about how to treat this virus, and mortality rates for hospitalized patients were greater than 10%.
- As the pandemic has worn on, it has become clear that the death rate from COVID-19 is less than 1% of those infected. Among those ill enough to be hospitalized, it is probably somewhere around 5%. 
Lesson 3: In illnesses with a high survival rate like COVID-19, it is difficult to prove treatment efficacy

- The greater the survival rate, the more difficult it is to show a survival benefit for a treatment.
- Since the survival rate is so high, it would likely take many thousands of patients enrolled in a randomized, double-blind, placebo-controlled study before any significant survival benefit could be shown. And since the survival rate is so high to begin with, any incremental survival benefit would likely be very small.
- This was why it was difficult to demonstrate futility of hydroxychloroquine for so long.
Lesson 3: In illnesses with a high survival rate like COVID-19, it is difficult to prove treatment efficacy.

- Remdesivir, which inserts itself in viral RNA and thus shuts down further replication of RNA, first showed promise as a treatment for Ebola virus, a virus that uses RNA as its genetic material. It is believed that the drug has a similar action against COVID-19, which is also an RNA virus.

- Remdesivir was better than placebo in shortening the time to recovery in patients hospitalized with COVID-19 illness. (Beigel, et al., NEJM, Nov 5, 2020)

- Survival benefit for Remdesivir falls just short of statistical significance (11% v. 15%. HR 0.52-1.03)
Lesson 3: In illnesses with a high survival rate like COVID-19, it is difficult to prove treatment efficacy

- Remember back in March 2020 when we thought you should avoid ibuprofen? That was to preserve inflammation and the immune response. Back in spring 2021 even for patients hospitalized with COVID-19 who had asthma or other steroid-responsive lung diseases, we avoided giving prednisone out of fear that the virus would reproduce unchecked.

- One major prospective, randomized study shows that 28-day mortality among patients with COVID-19 illness and on ventilators is reduced by about a third when dexamethasone is given. For patients on O2 but not intubated, the decrease is about 20%.

  (RECOVERY Collaborative Group, NEJM, Feb 25, 2021)
Lesson 4: The accuracy of antibody tests is like fishing
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- When antibody testing first became available, some news articles lauded the accuracy of these tests; others have portrayed them as no more accurate than a coin flip. Who is correct?
- Actually both are, and understanding the difference between specificity and positive predictive value helps us understand why.
- The sensitivity of a test is described as percentage of people with a disease who will have a positive test for that disease...important for screening for cancer.
- If one were searching for disease like one would fish for tuna, think of a high sensitivity test as a fishing net that effectively captures all tuna that come into contact with the net.
Lesson 4: The accuracy of antibody tests is like fishing

- Specificity, on the other hand, is defined as the percentage of people without a disease who will have a negative test. For tests with a potentially complicated follow up, like cardiac stress testing (which may be followed by cardiac catheterization), specificity is particularly important.

- If one were fishing for tuna, think of a high specificity test as a net that allows non-tuna to pass through.

- For available COVID-19 antibody tests, both the sensitivity and specificity are quite good, and this likely explains news reports lauding the accuracy of these tests. For most available tests, the sensitivity is 100%, and the specificity is over 99%.

- Positive predictive value takes into account the specificity of a test and the prevalence of a disease. The more prevalent a disease, the more likely an individual positive test is to be accurate.
Lesson 4:  The accuracy of antibody tests is like fishing

- Think of positive predictive value as the likelihood that an individual fish caught in our net is a tuna. If you are fishing off the coast of Maine, the prevalence of tuna is quite low, and that one individual fish is unlikely to be a tuna regardless of the ability of the net to capture tuna and the ability of non-tuna to pass through.

- If you are fishing in the Bahamas, where the prevalence of tuna is much higher, that individual fish is much more likely to be a tuna, regardless of the characteristics of the net.

- For our average Philadelphian last summer with 5% estimated prevalence of disease, with a test that has 99% specificity, the likelihood that a positive test actually represents disease is about 84%. If we have a test with 95% specificity (still pretty decent, one would think), that PPV drops to 51% (that coin flip that you may have read about).

- With increased seropositivity (now up to 30% in many cities) the PPV of antibody testing is much, much greater.

- NPV has moved in the opposite direction with increased seropositivity
Lesson 5: Air currents let you get away with it
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- The predominant spread of COVID-19 illness appears to be via respiratory droplets. These are droplets of saliva and/or mucus, anywhere from 5 to 1000 millionths of a meter in diameter.

- These droplets are large enough that the force of gravity pulls them to the ground relatively quickly, as they are generally not able to ride air currents for long periods of time.

- A secondary, probably much less significant cause of spread of COVID-19 illness is by airborne spread, or through aerosols. For droplets smaller than 5 millionths of a meter (the definition of an aerosol), the weight is small enough that aerosols can become suspended on air currents, and thus travel farther than respiratory droplets.

- However, because aerosols are so small, they carry much less virus.
Aerosol spread was probably a contributor to that super spreader event at a church choir in Seattle in March, but overall it appears that aerosol spread is far less important than spread through larger respiratory droplets.

It is generally agreed that it takes inhalation of a few hundred to a few thousand viral particles to cause an infection with COVID-19. Anything less is generally handled by the immune system before infection can occur.

A respiratory droplet of 100 millionths of a meter diameter has a volume that is 8,000 times that of an aerosol with a diameter of 5 millionths of a meter, and thus it can carry 8,000 times as much virus.

Because large respiratory droplets have so much more volume and can hold so much more virus, they are much more potent in causing infection. Much smaller aerosols, although better travelers, deliver much, much smaller packages of virus and are less dangerous.
Lesson 5: Air currents let you get away with it

- One study looking at over 7000 outbreaks of COVID-19 in China found that only one outbreak, involving two people, occurred outdoors. (Qian, et al.)

- It probably comes down to this crass example: if you find yourself in a situation where you could pass gas and reliably get away with it, you’re probably in a pretty safe environment, with sufficient spacing and ventilation.
Lesson 6: Vitamin D and COVID-19
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- To produce active Vitamin D, many well-functioning systems are necessary. First, the action of sunlight on the skin provides an important first step in making vitamin D. An important next step requires a healthy liver, and a final step requires healthy kidneys. A defect anywhere along this pathway can cause a deficiency in active vitamin D.

- In recent years, vitamin D supplementation has been demonstrated to reduce falls and fractures in elderly adults. Vitamin D deficiency has been linked to conditions as varied as cardiovascular disease, colon cancer, and depression.

- However, supplementation with vitamin D has not been shown to reduce the incidence of any of these “non-bone” conditions.
Lesson 6: Vitamin D and COVID-19

- Multiple studies appear to show a relationship between low vitamin D levels and infection with COVID-19. (Meltzer, et al.)
- Other articles in pre-publication suggest an increased risk of hospitalization, going to the intensive care unit, and death.
- At this point it remains unclear whether vitamin D deficiency is simply a marker for poor health and therefore associated with bad outcomes from COVID-19, or whether vitamin D supplementation may be useful to prevent infection and improve outcomes for people who are infected with the virus.
- The relationship between Vitamin D deficiency and worsened outcomes with COVID-19 is likely a correlation (reflecting other risk factors we’re aware of) rather than causation.
STOP COVID-19

HANDS | ELBOW | FACE | SPACE | HOME
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WASH THEM OFTEN | COUGH INTO IT | DON'T TOUCH IT | SAFE DISTANCE 3-6 FT | STAY HOME STAY SAFE
Lesson 7: Historically, viral pandemics proceed in waves
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- The 1918-19 influenza epidemic occurred in three major waves in the United States.
- The first occurred in the early spring of 1918, when soldiers training in the US and some returning from Europe spread what was a relative mild, novel H1N1 flu home. Deaths were minimal and receded by the summer.
- In October and November 1918, the death rate peaked, spurred on by large events like parades celebrating the end of WWI on November 11 and more mixing of returning troops.
Lesson 7: Historically, viral pandemics proceed in waves

- Social distancing measures helped decrease spread for a few months, but when a war- and flu-weary American public relaxed those measures, a second, lesser spike occurred in early 1919.
- Other, local spikes of the H1N1 occurred well into 1920, including a significant spike in New York City in 1920.
- Vaccination is the difference with our pandemic.
To Prevent Influenza!

Do not take any person’s breath.
Keep the mouth and teeth clean.
Avoid those that cough and sneeze.
Don’t visit poorly ventilated places.
Keep warm, get fresh air and sunshine.
Don’t use common drinking cups, towels, etc.
Cover your mouth when you cough and sneeze.
Avoid Worry, Fear and Fatigue.
Stay at home if you have a cold.
Walk to your work or office.
In sick rooms wear a gauze mask like in illustration.