



LIFESTYLE, NUTRITION &
SUPPLEMENTATION FOR
IMMUNE SUPPORT

DISEASE PHYSIOLOGY

We are in unprecedented times with the advent of the Novel Coronavirus, Covid-19. Before we dive into lifestyle, nutrition and supplementation, let's first better understand this disease

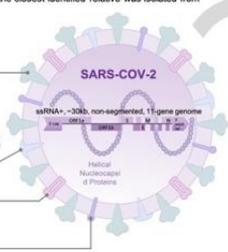
Disease Physiology

COVID-19: Coronavirus Disease 2019

Harvard Medical School Module 1: From Bench to Bedside Graphic Summary

VIROLOGY

SARS-CoV-2 is a new virus belonging to the Coronavirus family, which includes less pathogenic strains responsible for the common cold, as well as the viruses responsible for SARS and MERS. It is genetically related to the coronavirus responsible for the SARS outbreak in 2003; the closest identified relative was isolated from bats.



Spikes (S) glycoprotein

- Trimeric structure resembling corona or crown
- Responsible for receptor binding, membrane fusion, and hemagglutinin activity
- Target for eliciting host neutralizing antibody
- Unique SARS-CoV-2 polymorphism enables S activation by human furin protein (found in lungs, liver, and small intestine), which may explain the association of COVID-19 with liver failure

Hemagglutinin-esterase (HE) protein

Matrix (M) transmembrane glycoprotein

- Most abundant structural protein
- Determines shape of viral envelope

Envelope (E) protein

- Interacts with M to form viral envelope
- Important for virus infectivity

Transmission

- SARS-CoV-2 is spread primarily via droplet, though it can be aerosolized and can persist on plastic and stainless steel surfaces for up to 72h
- Disinfectants with commercial concentrations of EIOH or H₂O₂ are effective

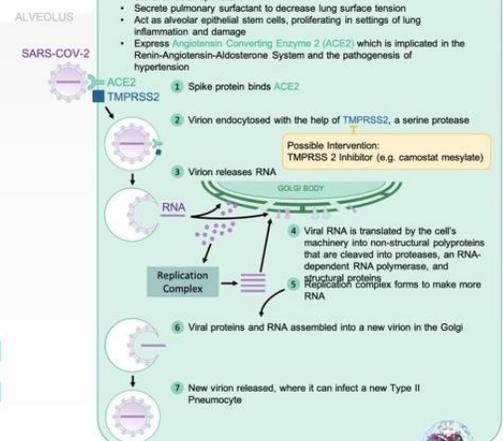
PATHOPHYSIOLOGY

Type I Pneumocyte

- Simple squamous epithelial cell
- 97% of alveolar epithelium
- Thin. Ideal for blood-gas barrier to adjacent pulmonary capillary endothelium

Type II Pneumocyte

- Cuboidal epithelial cell
- 3% of alveolar epithelium
- Secrete pulmonary surfactant to decrease lung surface tension
- Act as alveolar epithelial stem cells, proliferating in settings of lung inflammation and damage
- Express **Angiotensin Converting Enzyme 2 (ACE2)** which is implicated in the Renin-Angiotensin-Aldosterone System and the pathogenesis of hypertension



Immune Response

Innate Immune System

- Delayed or suppressed Type I Interferon (IFN) response during initial infection
- Viral replication triggers hyperinflammatory conditions and cytokine storm
- Influx of activated neutrophils and inflammatory monocytes/macrophages
- Serum neutrophilia and elevated pro-inflammatory cytokines are associated with severity of disease

Adaptive Immune System

- T helper cells Th1/Th17 are induced
- Specific antibodies not yet established
- Serum lymphopenia may be related to an antiviral response of bone marrow suppression

CLINICAL

Symptoms

Fever, 87.9% (only 44% at time of diagnosis)
Dry cough, 67.7%
Fatigue, 38.1%
Sputum production, 33.4%
Dyspnea, 18.6%
Myalgia/Arthralgia, 14.8%
Sore throat, 13.9%
Headache, 13.6%
Chills, 11.4%
Nausea/Vomiting, 5%
Nasal congestion, 4.9%
Diarrhea, 3.7%

Risk stratifying factors:

- Cardiovascular disease
- Hypertension
- Diabetes
- Chronic Respiratory Disease
- Cancer (any)
- Elderly, generally >60y
- Immunocompromised status

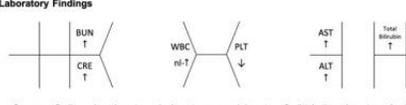
Full mechanisms not yet known

- Partially mediated by: ACE Inhibitor use, Angiotensin II Receptor Blocker use, Thiazolidinedione use, Ibuprofen use
- Upregulation of ACE2 Receptor
- Increased viral susceptibility

Diagnostic testing

- Currently a syndromic diagnosis of COVID-19 while awaiting definitive microbiological diagnosis
- RT-PCR against SARS-CoV-2 transcripts is the current gold standard diagnostic
 - High specificity
 - Variable sensitivity based on testing kit
- Serological antibody tests are in development and may detect both active and prior infection

Laboratory Findings



- Common findings: lymphocytopenia (most common laboratory finding), thrombocytopenia, leukopenia, TCRP (ARDS), septic shock
- Less common findings: TAST, TALT, TCK, TD-dimer
- In severe cases: Troponin, Tmyoglobin, TIL-6, Trocalcitonin, TLDH, lalbumin

Imaging

- Imaging is not recommended for screening, but common chest CT findings include ground-glass opacities, consolidation, and crazy paving patterns, in a bilateral peripheral distribution

Clinical Course

- Clinical outcomes: mild disease, pneumonia, severe pneumonia, acute respiratory distress syndrome (ARDS), septic shock
- Case fatality rate (CFR) estimated at 2%, but given that many mild cases have gone undiagnosed, CFR is likely lower

Investigational Treatment

- There are currently no FDA-approved treatments directed against COVID-19 at this time (03.19.20). However, a variety of therapies are under investigation. These include repurposing of
 - Antivirals: remdesivir, lopinavir/ritonavir
 - Antimalarials: chloroquine/hydroxychloroquine
 - Immunosuppressive medications: tocilizumab
 - Transfusing antibodies against SARS-CoV-2 analogs/SARS-CoV

Investigational Prevention

- It is expected that COVID-19 vaccine development will take a minimum of one year

	SYMPTOMS	MANAGEMENT
MILD	<ul style="list-style-type: none"> • Subjective or low-grade fever • Dry cough • Myalgias and arthralgias • Nasal congestion • Headache • Sore throat 	<ul style="list-style-type: none"> • 14d home quarantine • Return precautions • Supportive care: encourage eating and drinking, acetaminophen for comfort/fever • Avoid or be cautious with ibuprofen
MODERATE	<ul style="list-style-type: none"> • High-grade temperatures • Shortness of breath/trouble breathing especially if involving the need for supplemental oxygen • Profound fatigue 	<ul style="list-style-type: none"> • Airborne isolation • Supportive care: conservative fluid management, acetaminophen for comfort/fever • Respiratory support • Treat comorbidities: <ul style="list-style-type: none"> • Suspected sepsis: empiric antibiotics • Flu: oseltamivir • Asthma/COPD: bronchodilators
SEVERE	<ul style="list-style-type: none"> • Severe dyspnea • Hypoxia • Dehydration 	<p>As above plus:</p> <ul style="list-style-type: none"> • Advanced ventilatory support

tinyurl.com/MedStudentCOVID19Curriculum | tinyurl.com/MedStudentCOVID19Graphic
Figures not to scale. | Current as of 03.19.2020. | Please see bibliography in written module.
 Student authors: Adi Achanta; Kendall Carpenter; Pamela Chen; Nicole Gilette; Pinky Langat, PhD; Blake Oberfeld; Jordan Said; Simone Sasse; Abigail Schiff, PhD; and Allen Zhou | Graphic by Blake Oberfeld

Possible Lab Considerations for Practitioners:

1. See the appropriate provider. Get tested or go to the hospital. Maintaining hygiene is critical.

Diagnostics and Exam for Practitioners:

1. CXR- bilateral interstitial pneumonia (anecdotally starts most often in the RLL).
2. The hypoxia does not correlate with the CXR findings. Their lungs do not sound bad. Keep your stethoscope in your pocket and evaluate with your eyes and pulse ox.
3. Labs - WBC low, Lymphocytes low, platelets lower than their normal, CRP and Ferritin elevated most often. CPK, D-Dimer, LDH, Alkaline Phosphatase /AST/ALT commonly elevated. There should be caution about CT PE. These patients can have hypoxia hypoxia. The patients receiving IV contrast are going into renal failure and on the vent sooner.
4. Basically, if you have a bilateral pneumonia with normal to low WBC, lymphopenia, normal procalcitonin, elevated CRP and ferritin- you have covid-19 and do not need a nasal swab to tell you that, but should confirm anyway.
5. A ratio of absolute neutrophil count to absolute lymphocyte count greater than 3.5 may be the highest predictor of poor outcome. the UK is automatically intubating these patients for expected outcomes regardless of their clinical presentation.
6. An elevated Interleukin-6 (IL6 - CRP) is an indicator of their cytokine storm. If this is elevated watch these patients closely with both eyes. Watch Ferritin closely.
7. Other factors that appear to be predictive of poor outcomes are thrombocytopenia and LFTs 5x upper limit of normal.

THE IMPORTANCE OF A HEALTHY LIFESTYLE & DIET

Maintaining a healthy lifestyle and diet is always essential, but even more so now.

LIFESTYLE RECOMMENDATIONS

Get Adequate Sleep

When we sleep, our body repairs itself. Keep in mind when we are young, our body tends to produce ample amounts of the hormone melatonin. There is conjecture that one of the influencing reasons older adults are more vulnerable to Covid-19 or many diseases it is because

they typically produce much less melatonin and therefore, get less sleep. There are other Catecholamine's present in this reaction along with adequate Tryptophan levels, If you are having difficulty sleeping, you may want to talk to your healthcare provider about adding a melatonin supplement to your regimen.

Better Manage Stress

Stress induces inflammation in the body, which creates a greater vulnerability to Covid-19 or infectious disease. And with family and business routines in flux with many "stay at home" orders, you may be experiencing more stress than usual. Consider the following activities to help you better manage your day to day stress: Stress reduction will lower your IL-1 and IL-6 and possibly dysregulate your Th-17 responses and dysregulate your immune responses and perpetuate and cytokine barrage or storm.

1. **Begin a Meditation Practice:** If you've never meditated before this may feel daunting. Keep it simple. Try some different guided meditations available for free on YouTube to start.
2. **Deep Breathing:** Dr. Andrew Weil's 4-7-8 Breathing Technique is very simple and actually helps to ground your central nervous system and effectively manage stress. Try it [HERE](#).
3. **Seek Community:** Many of us may be isolated, so finding connections online is essential to not feeling alone. Your mental health is especially important during this time. Connect with loved ones, friends and co-workers via Skype or Zoom. Have your young children visit with their grandparents via Skype or Zoom and keep everyone safe. Seek out groups and forums online to connect with others as well. And be sure to maintain positive communication with those you are living with day to day.
4. **Journal:** If you're struggling with negative emotions, it's important to release them. Write down what you are feeling, including anger, fear, anxiety, etc. Once you've gotten these thoughts out of your head and onto paper, release them by tearing up the paper or burning it safely.
5. **Keep Yourself Busy:** If you have too much time on your hands, it's best to tackle those projects around the house you've been too busy to do. Now is the time! Organize closets, go through old photo albums, clean out your garage. Feeling productive does wonders for your mental health.

Spend Time in Nature

Carve out time each day to take a walk or bike ride outside. Even something as simple as sitting or walking in the grass can be very grounding, not to mention the Vitamin D your body naturally creates with the help of the sun.

FOODS THAT NOURISH

"Stress Eating" is a real thing And is absolutely something you want to curtail in times like this. A bit of comfort food here and there is one thing, just make sure that does not become your diet focus.

Skip the processed and pre-packaged boxed, bagged and canned foods. Frozen meals are also often high in sodium and not the best choice.

Focus on whole, fresh, organic foods whenever possible. Frozen foods should be your next best choice, as they are typically frozen at their peak of ripeness.

Fill your cart with fresh vegetables, greens, fruits and lean animal protein choices. Include high quality wild caught seafood and fish, as well.

Should you need to focus on foods that have a longer shelf life, consider:

Fruits with longer shelf life: Apples, oranges, lemons, and limes. Fresh bananas and berries can be easily frozen before going bad.

Vegetables with a longer shelf life: Root vegetables like onions, potatoes, sweet potatoes, carrots, and squash are all good choices.

If you're healthy and your body tolerates them, include nuts, seeds, rice, quinoa, beans, lentils and eggs. And don't forget healthy fats like olive oil, olives, and avocados.

Other items to consider keeping on hand include: jarred sauces and salsas, canned tuna/salmon, shelf stable milk, soups, broths, herbs and spices.

Foods that have specific characteristics and may be beneficial now include:

- Garlic
- Berries
- Broccoli and other cruciferous vegetables
- Avocado
- Chili Peppers
- Grapes
- Citrus Fruits
- Oysters
- Watermelon
- Spinach
- Ginger
- Turmeric
- Green Tea
- Caffeine in one cup of coffee

**** If you suffer from any food sensitivities, intolerances or allergies, now is not the time to test those. Please continue to follow your practitioner's advice and only consume items you know work well with your body and system.**

SUPPORTIVE SUPPLEMENTATION

Adding appropriate supplements can be very helpful as well. However, before adding any supplements to your regimen, please consult your physician to ensure there are no interaction issues with any medications or diagnosis you may have.

Zinc: Various viruses appear to be susceptible to the viral inhibitory actions of zinc. Zinc may prevent entry into cells and appears to reduce virulence.

Reducing NLRP3 inflammasome signaling, and consequently NFkB, TNF- α , IL-6, IL1B and IL-18 expression is a goal. Some products that may help.

1. baicalin and wogonoside
2. Licorice
3. nuts, and berries
4. Apigenin
5. flavonoids, ascorbic acid inhibits NLRP3 inflammasome activation.

Clinical trials have found that **vitamin C** shortens the frequency, duration and severity of the common cold and the incidence of pneumonia. Typical daily dosing of vitamin C ranges from 500mg to 3000mg daily with even higher doses utilized during times of acute infection.

Melatonin: Melatonin has been shown to inhibit NFkB activation and NLRP3 inflammasome activation. In fact, the age-related decline in melatonin production is one proposed mechanism to explain why children do not appear to have severe symptoms and older adults do. Melatonin also reduces oxidative lung injury and inflammatory cell recruitment during viral infections.

Elderberry: Elderberry appears most effective in the prevention or early stage of respiratory virus infections. It increases inflammatory cytokines, including IL-1B so should be discontinued with symptoms of infection (or positive test). An evidence-based systematic review of elderberry conducted by the Natural Standard Research Collaboration concluded that there is level B evidence to support the use of elderberry for influenza²⁵ which may or may not be applicable to COVID-19 prevention.

Vitamin D: In certain conditions, vitamin D has been found to decrease NLRP3 inflammasome activation and vitamin D receptor activation reduces IL-1b secretion. However, 1,25(OH)vitamin D has also been found to increase IL-1b levels, and should, therefore, be used with caution and perhaps discontinued with symptoms of infection. It's Impact on ACE receptors or type II alveolar receptors is unfounded.

DURING SYMPTOMS OF INFECTION OR POSITIVE TEST:

Given the critical role of inflammatory cytokines (namely IL-1B and IL-18) in the

pathogenicity of infection, as well as the impossibility of predicting which individuals are susceptible to the “cytokine storm”, technically called secondary hemophagocytic lymphohistiocytosis, or sHLH, it appears to be prudent to avoid high and regular use of immunostimulatory agents which could physiologically enhance these cytokines.

Again, in the absence of human clinical data, **caution is warranted with the following immune activating agents** due to preclinical evidence of increased IL-1B and/or IL-18 production in infected immune cells.

- Elderberry
- Polysaccharide extracts from medicinal mushrooms (Cooked)
- Echinacea
- Vitamin D

Below is a list of nutrients that, according to research, may be beneficial. Please work with a licensed practitioner to determine proper dosing for your unique situation.

Please be aware that different stages of a condition may be more conducive to a nutrient. Please be aware of this. There are many good nutrients not on this list, but we are avoiding them. Some nutrients are good immune-enhancers, but as a result of a cytokine barrage from a super antigen, some immune enhancers and even Th-1 activators are avoided unless you can counter that effect with another nutrient. These barrages of cytokines are not as a direct result of the nutrient given per say, but we want to err on the side of cautions as it pertains to common sense and the mechanism of some infestations. COVID-19 being one of them.

- Vitamin C (Multiple varieties)
- Vitamin A
- Vitamin E
- Vitamin D (Before infection confirmation)
- Vitamin B6 (Monitor levels or use P5P)
- Probiotics
- Licorice Root
- Olive Leaf
- Zinc Glycinate Chelate
- S-Acetyl Glutathione or Liposomal Glutathione
- Lysine
- IgY (Hyperimmunized Egg Immunoglobulins)
- 1, 3/1, 6 beta-glucan from yeast Saccharomyces
- Sulforaphane
- Andrographis
- Astragalus
- Lions Mane
- Apigenin
- Curcumin (Not Black Pepper)
- Baicalin
- Quercetin
- Trans-Resveratrol

