The Coronavirus Disease 2019 (COVID-19) pandemic has had massive, overarching ramifications for our global population. This is an unprecedented time for our healthcare system, and as medical trainees ourselves, we felt an obligation to synthesize the growing literature and educate our peers.

This first module, written by students for students, is designed to walk you through the disease characteristics of COVID-19, including the basic virology of SARS-CoV-2 (the etiologic agent of COVID-19) and clinical knowledge to date. We hope that a deeper understanding of the pathophysiology of the virus, including its structure, transmission, and host immune defenses, will allow you to critically engage with evolving diagnosis, treatment, and prevention efforts. Throughout, we will highlight areas of ongoing investigation and innovation, from bench to bedside. This information will help you tackle the subsequent modules which discuss epidemiology (Module 2), the current situation and healthcare response (Module 3), and communication with the general public (Module 4). We expect that this module will take 2 hours to complete.

OVERARCHING LEARNING GOAL:
● Evaluate how the emerging understanding of COVID-19 pathophysiology translates to evolving diagnosis, treatment, and prevention efforts

LEARNING OBJECTIVES:
At the end of this module, medical students should be able to:
● Relate the basic virology of SARS-CoV-2 to evolving COVID-19 diagnosis and prevention approaches
● Translate knowledge of the host immune response against SARS-CoV-2 to COVID-19 risk stratification, treatment, and vaccine strategies
● Build a differential diagnosis for COVID-19 using its typical clinical manifestations, laboratory, and imaging findings
● Evaluate current triage and treatment recommendations for COVID-19, stratified by disease severity
● Appreciate how COVID-19 pathophysiology underlies ongoing research into investigational therapeutics and vaccines
BASIC VIROLOGY AND IMMUNOLOGY:

Basic Virology

Introduction

In December 2019, a series of cases of pneumonia of unknown origin were reported in Wuhan, the capital city of Hubei province in China. The causative virus was isolated and characterized in January 2020 (Zhou et al., Nature 2020, Zhu et al., NEJM 2020). On January 12, 2020 the World Health Organization (WHO) tentatively named the virus as the 2019 novel coronavirus (2019-nCoV). On January 30, 2020 WHO issued a public health emergency of international concern (PHEIC) and on February 11, 2020, the WHO formally named the disease caused by the novel coronavirus as coronavirus disease 2019 (COVID-19). At that time, based on its genetic relatedness to known coronaviruses and established classification system, the International Committee on Taxonomy of Viruses classified and renamed 2019-nCoV as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On March 11, 2020, the WHO formally characterized the global spread of COVID-19 as a pandemic, the first to be caused by a coronavirus.

Classification

Coronaviruses are positive-sense, single-stranded enveloped RNA viruses with helical capsids that infect a wide range of hosts including humans, bats, other mammals, and birds. As shown in the schematic taxonomy below, coronaviruses are classified within the order Nidovirales and are further subclassified into four genera: alpha, beta, delta, and gamma coronaviruses, of which alpha and beta coronaviruses are known to infect humans. As a family, coronaviruses most prominently include several human coronaviruses (HCoV) that are associated with lower pathogenicity (HCoV-229E, -NL63, -OC43, -HKU-1), contributing to seasonal cases of the ‘common cold’ and sometimes linked to more severe respiratory illness (Bradburne et al., BMJ 1967; Lieberman et al., Chest 2010). Two betacoronaviruses have previously been identified to cause more severe disease and outbreaks: severe acute respiratory syndrome coronavirus (SARS-CoV), responsible for the SARS worldwide outbreak in 2002-3 with 8,096 cases and 774 deaths reported, and Middle East respiratory syndrome coronavirus (MERS-CoV), responsible for 2,102 cases and 780 deaths reported during the 2012 MERS outbreak. SARS-CoV-2 falls under the betacoronavirus genus and is the seventh coronavirus identified to infect humans (Zhou et al., Nature 2020, Zhu et al., NEJM 2020).
Schematic of Baltimore classification scheme based on type of genome and replication for virus families (text in blue), highlighting SARS-CoV-2 and select virus families with viruses (influenza virus, rhinovirus) known to cause common human respiratory infections. Adapted from Collier, Oxford, Kellam, Human Virology 5e 2016.

Genome

Coronaviruses have the largest genome of all ribonucleic acid (RNA) viruses infecting humans, consisting of a positive-sense single-stranded RNA roughly 30 kb in size that is 5’-capped and 3’-polyadenylated. Shown in the figure below, the virus genome is non-segmented and produces polyproteins initially. There are a total of 11 genes. The genome is organized with non-structural polyproteins, which are then cleaved to be enzymes such as proteases and RNA polymerase, encoded at the 5’ end and structural proteins encoded toward the 3’ end.

SARS-CoV-2 genomic organization and encoded proteins (Lu et al., Lancet 2020; genome assembly data). Figure adapted from Collier, Oxford, Kellam, Human Virology 5e 2016.
Genetic relatedness to other viruses and suspected origins

The majority of new coronaviruses are isolated from bats, which serve as a natural reservoir, though other animal species have been linked as intermediate hosts in the transmission to humans, such as the civet cat for SARS-CoV (Guan et al., Science 2003) and dromedary camel for MERS-CoV (Chu et al., Emerg Infect Dis 2014). As seen in the phylogenetic trees below, SARS-CoV-2 viruses isolated globally are genetically related to SARS-CoV isolates of the 2003 SARS outbreak. Currently, the closest identified relative to SARS-CoV-2 is a virus isolated in bats (Zhou et al., Nature 2020). It is suspected that an intermediate host may have facilitated the zoonotic event, given both overall limited interactions between bats and humans and also the initial cluster of cases which were epidemiologically linked to a live animal and seafood market in Wuhan. Among a large variety of animals present, the pangolin, a scaly anteater and commonly trafficked mammal, has been implicated as a potential intermediate host, based on high levels of similarity of pangolin coronaviruses to SARS-CoV-2 at the protein level (Lam et al., bioRxiv preprint 2020). However, full genome analysis of pangolin coronaviruses have appeared more distinct (Liu et al., bioRxiv preprint 2020), suggesting that other market animals, such as civets or pigs, may have been the intermediate host between bats and humans (Lu et al., Lancet 2020; Zhang et al. Clin Infect Dis 2020).
Phylogeny showing relatedness of ‘SARS-like’ betacoronaviruses (‘Sarbecovirus’ subgenus from previous figure) to select SARS-CoV-2 samples isolated from China, USA, and Japan. Each circle ‘tip’ of the phylogenetic tree represents a virus sample, color coded by type of host. From nextstrain. For more information on how to read phylogenetic trees see here.

**Thought questions:**

Based on the phylogeny, would you expect SARS-CoV-2 to behave more like SARS-CoV or MERS-CoV?

What are some benefits and drawbacks of analyzing specific genes compared to the whole genome of a virus?

How might understanding the origin and intermediate hosts of a virus influence human practices and policies to prevent zoonotic viruses from seeding new epidemics?

**Virus structure**

Microscopically and as seen in Figure 3, coronaviruses have club-shaped trimeric surface spike glycoproteins that give the virions the appearance of a crown, hence their name (from the Latin *corona* meaning “crown”). Summarized in Table 1 below, coronaviruses contain four major structural proteins: the spike (S), membrane (M), hemagglutinin-esterase (HE) in some betacoronaviruses, and envelope (E) all located on the membrane envelope, and the nucleocapsid (N) protein found in the core. The N proteins associate with the RNA genome to form a long helical ribonucleoprotein (RNP) packaged within the enveloped virus particle. The M protein, the most abundant of the structural proteins, is a transmembrane glycoprotein that gives the envelope its shape. The E protein is thought to be critical for coronavirus infectivity.

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Last updated 3/20/2020

<table>
<thead>
<tr>
<th>Structural Protein</th>
<th>Protein Function and Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleocapsid protein (N)</td>
<td>• Binds with RNA genome to make helical ribonucleoprotein</td>
</tr>
<tr>
<td>Membrane protein (M)</td>
<td>• Transmembrane envelope protein</td>
</tr>
<tr>
<td></td>
<td>• Determines shape of viral envelope</td>
</tr>
<tr>
<td>Envelope protein (E)</td>
<td>• Interacts with M protein to form viral envelope</td>
</tr>
<tr>
<td></td>
<td>• Important for virus infectivity</td>
</tr>
<tr>
<td>Spike protein (S)</td>
<td>• Binds to host cell receptors to facilitate entry into host cells</td>
</tr>
<tr>
<td></td>
<td>• Targeted by host neutralizing antibodies</td>
</tr>
</tbody>
</table>

The S surface protein is responsible for receptor binding, host range, membrane fusion, hemagglutinin activity, and is a target for eliciting host neutralizing antibodies (*Millet & Whittaker, Virus Res 2015*). SARS-CoV-2 has genetic polymorphisms in the S protein when compared to other coronaviruses that can cause lethal human disease, such as SARS and MERS coronaviruses. This different spike protein structure has suggested that protein can be activated by furin, a host-cell enzyme, found in many human tissues including lungs, liver, and small intestines (*Andersen et al., Nature 2020*). Whereas SARS-CoV and other related coronaviruses do not have furin activation sites, potential furin activation for SARS-CoV-2 may explain its expanded cellular tropism (*Walls et al., Cell 2020*), which may contribute to the manifestation of liver injury with COVID-19 (*Zhang et al., The Lancet 2020*).
Alignment of amino acid sequences highlights differences between SARS-CoV-2 to SARS-like coronaviruses and SARS-CoV in spike protein residues important for (a) receptor-binding and (b) polybasic cleavage site for potential furin activation. Figure modified from Andersen et al., Nature 2020.

_thought questions:_

How could the specific proteins (S, E, M, and N) on SARS-CoV-2 be useful targets for diagnosis? For treatment? What technologies or molecular diagnostics/therapeutics would be useful?

Pathogenesis of COVID-19 Infection

Research is ongoing to characterize the pathogenesis of how SARS-CoV-2 results in COVID-19 disease in humans. Below is our current understanding of the literature.

Viral entry

Two types of epithelial cells make up the lining of the airways at the level of the alveoli. Type 1 pneumocytes are simple squamous epithelial cells that collectively make up 97% of alveolar epithelium; they are thin and form the blood-gas barrier adjacent to the pulmonary capillary endothelium. In contrast, type 2 pneumocytes are cuboidal epithelium, and make up only 3% of the alveolar epithelium. They secrete pulmonary surfactant (dipalmitoyl phosphatidylcholine) to decrease the surface tension of the lungs, and also act as stem cells for the alveolar epithelium. They proliferate in the setting of lung inflammation and damage to regenerate alveolar tissue.

SARS-CoV-2 enters host cells through interacting with ACE2, a transmembrane protein on type 2 pneumocytes in the alveoli and intestinal epithelial cells. ACE2 is implicated in the renin-angiotensin-aldosterone system (RAAS) and the pathogenesis of hypertension. Of note, ACE2 is a distinct enzyme from the ACE that converts angiotensin I to angiotensin II in the lungs as part of RAAS. While ACE acts to generate angiotensin II, a potent vasoconstrictor that will increase systemic vascular resistance and drive the synthesis of aldosterone, ACE2 instead acts in the opposite direction to convert active angiotensin II to angiotensin 1-7. This functions as negative regulation of RAAS, as ACE2 both decreases the concentration of Ang II and produces a primary vasodilatory agent (Ang 1-7). ACE2 is an interferon-induced gene and in addition to type 2 pneumocytes is expressed on intestinal epithelial cells and nasal goblet secretory cells (Ziegler et al., Cell preprint 2020). SARS-CoV-2 mainly infects type 2 pneumocytes in the lung (Zhu et al., NEJM 2020), but has also been found inside intestinal epithelial cells (Xiao et al., Gastroenterology 2020).
Binding of the SARS-CoV-2 S protein to ACE2 triggers a conformational change in the viral S protein, allowing for proteolytic digestion by host cell proteases (Zhou et al., Nature 2020). TMPRSS2 is a serine protease on the host cell membrane that primes the viral S protein by cleaving it, which allows fusion of the viral and host cell membranes. The encoded TMPRSS2 protein contains a type II transmembrane domain, a receptor class A domain, a scavenger receptor cysteine-rich domain and the serine protease domain. Both SARS-CoV and SARS-CoV-2 use the ACE2 receptor for entry and are primed by TMPRSS2, and TMPRSS2 has been investigated as a therapeutic target. Experimental use of an inhibitor of TMPRSS2, camostat mesylate, decreased the infectiousness of virus particles with coronavirus surface proteins in cell culture (Hoffmann et al., Cell 2020).

Upon entering in a membrane vesicle, the virion fuses with the vesicle and releases its single segmented RNA genome into the cytosol. Since the virus is positive-sense, it can essentially serve as mRNA and be translated immediately into viral proteins by the endogenous cell machinery; some of these proteins form a replication complex to produce more RNA with a viral RNA-based RNA polymerase for building up more SARS-CoV-2 virions to be released from the cell. Within the cytosol, positive-sense RNA and viral proteins form a virion, which fuses with the cell membrane and is released to infect further cells.

**Hijack**

How SARS-CoV-2 replicates itself in the cells of those infected

1. Spike protein on the virion binds to ACE2, a cell-surface protein. TMPRSS2, an enzyme, helps the virion enter.
2. The virion releases its RNA.
3. Some RNA is translated into proteins by the cell’s machinery.
4. Some of these proteins form a replication complex to make more RNA.
5. Proteins and RNA are assembled into a new virion in the Golgi.
6. Released.

Sources: Song et al., Viruses, 2019; Jiang et al., Emerging Microbes and Infections, 2012; The Economist

Demonstration of how SARS-CoV-2 infects type 2 pneumocytes, propagates its own mRNA and viral proteins with host machinery, and then releases newly formed SARS-CoV-2 virions. From The Economist.

**Thought question:**
What are the pros and cons of targeting human proteins compared to viral proteins to treat a viral disease?

**Transmission dynamics**

Transmission of SARS-CoV-2 is thought to occur mainly through respiratory droplets (Aylward et al., Report of the WHO-China Joint Mission 2020). Other routes of transmission such as virus contamination of
common objects, aerosolization in a confined space, or spread from asymptomatic infected persons have been suggested, though the significance of their role in contributing to overall transmission have yet to be fully elucidated (Cai et al., Emerg Inf Dis 2020; Rothe et al., NEJM 2020). Respiratory droplets can be generated by sneezing (40,000 droplets), coughing (3,000 droplets), or talking (about 600 droplets per minute). They can also be produced by medical procedures like intubation and bronchoscopy or by use of oxygen masks and nebulizers (Tang et al., Journal of Hospital Science 2006). Larger droplets (>60 microns) tend to spread about 1 meter (3 feet) and require droplet precautions, while smaller ones spread further and require stricter airborne precautions. So far, it seems likely that SARS-CoV-2, like SARS-CoV, is mainly spread through larger droplets, rather than through the smaller droplets that would qualify it as an airborne pathogen, although the medical procedures mentioned above risk making it airborne with a larger radius of spread (Tang et al., Journal of Hospital Science 2006; Aylward et al., Report of the WHO-China Joint Mission 2020). However, this remains an area of active investigation.

A flash photo of a human sneeze. Source: Tang et al., Journal of Hospital Science 2006

Early reports indicate that SARS-CoV-2 has the potential to be transmitted through fomites, or objects with virus on their surface. SARS-CoV-2 appears to have similar viability in aerosols and on surfaces when compared to that of SARS-CoV. When aerosolized, SARS-CoV-2 remains viable for up to 3 hours, a critical consideration for hospital infection control, particularly when undergoing aerosolizing procedures. Viable SARS-CoV-2 was measured from surfaces up to 4 hours on copper, 24 hours on cardboard, and 72 hours on plastic and stainless steel (van Doremalen et al., NEJM 2020). While these results do not fully evaluate the infectivity of the virus on different surfaces, in general this data supports the notion that maintaining good hygiene (washing hands often, especially after touching public surfaces, and avoiding touching face and mouth) could help mitigate the spread of SARS-CoV-2. Moreover, this data suggests that other viral properties must explain the infectivity differences between SARS-CoV-2 and SARS-CoV. Previous work studying other coronaviruses have also suggested that surface disinfection such as with 62-71% ethanol or 0.5% hydrogen peroxide, commonly found in household cleaning products, can inactivate coronaviruses that persist on surfaces (Kampf et al., J Hosp Infect 2020).

As is suggested by the infection of intestinal epithelial cells, there is some evidence of live virus shedding in stool (Xiao et al., Gastroenterology 2020; Wang et al., JAMA 2020; Ong et al., JAMA 2020).
While there has been fecal-oral transmission of SARS, so far there have been no documented cases of fecal-oral transmission of COVID-19 (Aylward et al., Report of the WHO-China Joint Mission 2020).

Whether COVID-19 can be spread by vertical transmission, passed from mother to fetus or neonate during pregnancy or during the perinatal period, is not well understood. In a number of limited case series of pregnant women with lab-confirmed COVID-19, none of the infants were found to have COVID-19 and SARS-CoV-2 was not detected in samples including amniotic fluid, cord blood, neonatal throat swab, or breastmilk (Chen et al., Lancet 2020, Li et al., Emerg Infect Dis 2020). Previous limited case series have found infants born to mothers with SARS were negative for SARS-CoV (Wong et al., Am J Ob Gyn 2004; Shek et al., Pediatrics 2003) and vertical transmission with SARS or MERS infection have not been documented in the past (Schwartz & Graham, Viruses 2020). Neonatal cases of COVID-19 have been reported; however, these were complicated by close contact history with confirmed infected persons following birth (Qiao, Lancet 2020). There is currently limited evidence to suggest high risk of intrauterine transmission for COVID-19.

A feature of COVID-19 is its ability to be transmitted by asymptomatic individuals, whether before symptoms start or by individuals who do not have symptoms. Virus shedding can occur at least 24-48 hours before symptoms start (Aylward et al., Report of the WHO-China Joint Mission 2020), and has been shown in asymptomatic individuals (Zhou et al., NEJM 2020). Modeling of transmission events in China prior to the January 23rd travel restrictions estimated that undocumented cases, which experienced no to mild symptoms, were responsible for 79% of new cases (Li et al., Science 2020). Current estimates of the COVID-19 incubation period, which refers to the time period from initial exposure to symptom onset, range from 1-14 days with a median of 5 days and 95th percentile of 12 days, similar to SARS (Lauer et al., Ann Intern Med 2020; Li et al., NEJM 2020). The detection of SARS-CoV-2 RNA in patients at 20 days and as long as 37 days in one patient also suggests the potential of prolonged virus shedding (Zhou et al., Lancet 2020). Because they may shed virus for a period of time after symptoms have resolved, it is still unknown how long someone in remission from COVID-19 remains infectious. The delay between exposure and showing symptoms combined with transmission from asymptomatic hosts have made SARS-CoV-2 particularly difficult to contain.

Thought questions:

How would you predict that a difference in infected cell types might change the presentation and transmission of COVID-19?

Imagine a few real-life scenarios that you may soon encounter or may have already encountered:

Diane wants to order food from a delivery service, but is worried about getting sick. What advice would you give her about touching packages, meeting the delivery person, and ordering premade food?

Brian has a friend who had low fevers, fatigue, and a dry cough, but was never tested for COVID-19. His friend self-quarantined at home and now has not had any symptoms for the past day. Brian wants to hang out with this friend today. What would you tell him about his risk of exposure?

How do estimates of incubation periods and viral shedding inform public health efforts?
**Immune Responses in COVID-19**

*Innate immune response*

In severe cases of SARS and MERS, decreased viral control of SARS-CoV and MERS-CoV leads to an increase in neutrophils, monocytes and macrophages in the lung, which is associated with increased immunopathology. The influx of cells into the lungs is accompanied by a cytokine storm, with increases in levels of serum pro-inflammatory cytokines. In COVID-19, increases in neutrophils in the lungs are associated with severe disease ([Prompetchara et al., Asian Pacific Journal of Allergy and Immunology 2020](https://doi.org/10.22148/apiai.2020.35.4.347)). Higher serum pro-inflammatory responses seen in people with COVID-19 are associated with severity of disease ([Huang et al., Lancet 2020](https://doi.org/10.1016/S0140-6736(20)30699-6)).

**Thought question:**

How might the integrity of the lung and ability of immune cells to migrate to the site of infection affect the immune response to SARS-CoV-2?
Adaptive immune response

The adaptive immune response generally consists of humoral immunity, most prominently antibodies produced by B cells, and cellular immunity, including CD4+ and CD8+ T cells and NK cells. These cells are primed by antigen presentation from cells including dendritic cells, macrophages and B cells among others. There is a detectable humoral immune response to SARS-CoV-2, but the presence of a protective antibody response has not yet been established in animal models or in humans. When it comes to T cells, a Th1-type CD4+ T cell response is important in successful control of SARS-CoV and MERS-CoV (Li et al., J Imm 2008; Shin et al., Clin Inf Dis 2019). CD8+ T cell responses are also important to control infection, but may be associated with increased lung pathology in SARS and MERS when overabundant, making it difficult to discern cause from consequence (Shin et al., Clin Inf Dis 2019; Prompechatara et al., As Pac J of All and Imm 2020). MERS-CoV has been shown to decrease antigen presentation on dendritic cells and macrophages, delaying activation of the adaptive immune system (Shokri et al., J Cell Physiol, 2019). So far, this has not been studied in SARS-CoV-2. Lymphopenia is also seen in COVID-19; this may be due to bone marrow suppression by the antiviral response.

A key question for understanding the dynamics of the epidemic and whether a vaccine will be protective is whether previously infected individuals can be re-infected. A pre-print suggests that macaques are protected from subsequent SARS-CoV-2 infection (Bao et al., bioRxiv 2020). At least one case of human reinfection has been reported (Science Times, 2/27/20), although some experts dispute this finding (The Hill, 2/27/20). For more detailed information on vaccine development, see the below section. For more information about how this affects epidemiological modeling, see Module 2.

For more details on immune responses to SARS-CoV-2, please see an expanded version in the supplementary materials.

Thought question:
How might the initial mild presentation and later severe disease seen in COVID-19 be explained by the immune response to the virus?

Immune factors involved in outcome of infection

Many of the inflammatory markers discussed above have been investigated as possible predictors of disease mortality. See laboratory diagnostics below for more information.

Additional Readings:
Prompechatara et al., Asian Pacific Journal of Allergy and Immunology, 2020
de Wit et al., Nat Rev Microbiol 2016
CLINICAL PRESENTATION OF COVID-19

Clinical Presentation

Information regarding the clinical presentation of COVID-19 is continually evolving. Much of our understanding at this point comes from cohort studies of patients with COVID-19 out of China. The largest of these cohort studies being a report of 55,924 patients with laboratory confirmed COVID-19 (WHO-China Joint Commission Report, 2020). The most common signs and symptoms are detailed in the following graph:

Of note, though a majority of patients have fever at some point in their disease course, a study of 1,099 patients (both hospitalized and outpatient) with laboratory-diagnosed COVID-19 from 522 hospitals in 30 provinces of China found that only 44% of patients were febrile at the time of diagnosis, which highlights some of the diagnostic challenges associated with variable clinical presentations (Guan et al., NEJM 2020).

Thought questions:

Diane wakes up feeling “off,” and she calls her doctor to ask about the possibility of having coronavirus. If you were her doctor, what questions might you ask? What is on your differential alongside COVID-19? Does the lack of a fever mean a patient is not infected with SARS-CoV-2? Why not? What about the presence of a sore throat or nasal congestion? So if Brian is correct and the majority of people will have “just a bad cold” with fever, dry cough, and fatigue, why are we taking such drastic measures to contain this virus?

In summary, no ONE symptom or set of symptoms can reliably diagnose or exclude COVID-19 infection but it is clear that cough, fever, and fatigue are most commonly seen. While sore throat and nasal congestion, typical upper respiratory infection symptoms, have been seen in COVID-19 patients, they are less...
common and may suggest an alternate etiology, such as a viral pathogen that more commonly infects the upper respiratory tract or possible co-infection. As discussed in the basic virology section, it is also important to remember that a person begins shedding the virus (i.e. can transmit the virus to others) prior to symptom onset and some people will never develop symptoms and remain asymptomatic carriers (Li et al., Science 2020; Pan et al., Lancet 2020; Roth et al., NEJM 2020).

Children infected with COVID-19 are less likely to require hospitalization and ICU admission than their adult counterparts and have lower fatality rates (CDC MMWR, 3.18.20). This difference in disease severity among children and adults is poorly understood at this time, but is under active investigation. If you would like to know more about COVID-19 in children, please reference the supplemental materials, section COVID-19 and children.

Thought questions:
Why might infants and children infected with SARS-CoV-2 have more mild symptoms than in adults and be at a lower risk for progression to serious illness including pneumonia and acute respiratory distress syndrome (ARDS)?
(Note: there is currently no consensus on this topic, and it is still an area of active debate)
If symptoms are so mild in children, why are we closing schools?

Risk Stratification
The largest study from the Wuhan Pulmonary Hospital showed that several common chronic conditions have prognostic implications for patients with COVID-19, including hypertension, type II diabetes, and cardiovascular (as well as cerebrovascular) disease (see Figure 2 below from Osmosis).

<table>
<thead>
<tr>
<th>AGE, years</th>
<th>CASE FATALITY RATE, %</th>
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<tbody>
<tr>
<td>0-9</td>
<td>___</td>
</tr>
<tr>
<td>10-19</td>
<td>0.2</td>
</tr>
<tr>
<td>20-29</td>
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<tr>
<td>30-39</td>
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<tr>
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<td>70-79</td>
<td>8.0</td>
</tr>
<tr>
<td>&gt; 80</td>
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<table>
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<tr>
<th>COMORBID CONDITION</th>
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<tr>
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</tr>
<tr>
<td>DIABETES</td>
<td>7.3</td>
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<tr>
<td>CARDIOVASCULAR DISEASE</td>
<td>10.5</td>
</tr>
<tr>
<td>CHRONIC RESPIRATORY DISEASE</td>
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</tr>
<tr>
<td>CANCER (any)</td>
<td>5.6</td>
</tr>
<tr>
<td>NONE</td>
<td>0.9</td>
</tr>
</tbody>
</table>

This summary of a large study of patients in Wuhan in late 2019 and early 2020 demonstrated the above comorbid chronic conditions as having many folds higher risk for fatality in cases of COVID-19 confirmed by RT-PCR. In addition, age above 60 was
demonstrated to be an independent risk factor for COVID-19; it is worth noting that elderly patients are also more likely to have the aforementioned comorbid chronic conditions.

Osmosis: https://www.youtube.com/watch?v=JKpVMivbTfg

“Elderly” age has been found to be an independent risk factor for both COVID-19 infection and a more serious disease course (see above figure). While the precise age is up for debate, it is clear that the older a patient is (particularly above 60 years of age), the higher their mortality risk is. In addition to the increased case fatality rate, older age has also been associated with increased need for ICU admission in the US (albeit to a lesser extent than case fatality). It is worth noting, that although young people are commonly thought to be unaffected or very mildly affected by COVID-19, 38% of all patients requiring hospitalization due to COVID-19 in the US as of 3/16/20 were between ages 20-54 (CDC MMWR, 3.16.2020).

**FIGURE 2. COVID-19 hospitalizations,* intensive care unit (ICU) admissions,† and deaths,‡ by age group — United States, February 12–March 16, 2020**

(CDC MMWR, 3.16.2020)

Immunocompromised and immunosuppressed patients are considered to be at high risk for COVID-19 infection as well as fatality in confirmed cases. Data is currently lacking to characterize what precise clinical population should be considered: healthcare professionals and media are generally being cautious and telling people on any immunosuppressive agents for any reason that they are at higher risk for infection and possibly a more severe disease course. It is important to remember that many diseases are treated with immunosuppressive agents (corticosteroids such as prednisone as well as disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and anti-TNF agents are common), and thus the spectrum of significantly immunosuppressed patients may be large. Patients with primary immunodeficiencies are considered to be immunocompromised and also at theoretically higher risk for infection and fatality.
Diagnostics

Thought question:
Given that treatment for COVID-19 is primarily supportive, what are the benefits of testing for SARS-CoV-2? Given what you have learned about the basic virology of SARS-CoV-2, how would you design a test to look for infection? From where would you collect samples?

Molecular Assays

After the emergence of COVID-19, labs around the world rapidly began developing diagnostic tests for SARS-CoV-2, with most so far developing real-time RT-PCR techniques against the RNA-dependent RNA polymerase (RdRp), E (envelope), N (nucleocapsid), S (spike protein), and/or ORF1b transcripts (Video review of RT-PCR). The WHO initially dispatched 250,000 kits based on initial work from Christian Drosten (Institute of Virology, Charité University Hospital, Berlin) and collaborators in Europe and Hong Kong. The CDC then developed its own rRT-PCR diagnostic panel, though critical errors in primer development limited its scale-up and have caused testing shortages in the United States (review: Sheridan, Nature 2020). Several commercial laboratories are developing and distributing their own PCR diagnostic tests to meet this growing need (see Module 3).

Currently, all diagnostic tests use respiratory specimens, primarily from nasopharyngeal, and sometimes oropharyngeal, swabs. Although RT-PCR appears to be highly specific, sensitivities across kits vary dramatically, and can be as low as 70% compared against clinical suspicion with positive CT findings, especially early in the disease course (Fang et al., Rad 2020; Ai et al., Rad 2020). Given this higher likelihood for false negatives, if clinical suspicion remains for COVID-19 despite a negative initial test, the WHO recommends resampling and retesting from multiple sites. Additional PCR testing can be done on stool and urine samples, though whether this represents active infection or continued viral shedding is unknown.

The current status of PCR testing resources and guidelines will be discussed in Module 3.

Thought questions:
What are the limitations of testing via nasopharyngeal swab?
What might be the benefits of developing a serological test for SARS-CoV-2? How would you design a serological test, and what would you look for? (Hint: consider HIV and hepatitis panels)

Immunooassays

Serologic diagnosis was validated during the SARS epidemic with SARS-CoV (Woo et al., J Clin Microbiol 2004), and many hypothesize that similar serologic tests against COVID-19 specific antibodies or antigens could be used for SARS-CoV-2 (video review of ELISA, the primary method of antibody/antigen detection). Zhou and colleagues discovered that the blood samples of patients with COVID-19 mounted the expected dynamic pattern of IgM followed by IgG antibody levels against a bat SARSr-111 CoV Rp3 nucleocapsid protein (NP) antigen, at significantly higher levels than healthy patients (Zhou et al., Nature 2020, figure below). IgM/IgG testing thus could reveal not only those with active infection but also those with a missed previous infection, improving our epidemiological understanding of the disease (Sabeti,
A rapid diagnostic antibody test against the SARS-CoV-2 spike protein (both the full length protein, and its smaller receptor binding domain) has recently been designed and validated, and is awaiting FDA approval (Amanat et al., bioRxiv preprint 2020). The authors argue that obtaining blood rather than respiratory samples, especially if blood is collected by finger prick onto a paper strip, might also decrease risk of transmission to healthcare workers handling the specimens, and allow for rapid diagnostic turnaround. Of note, it still may take days before IgM antibodies are mounted against the virus in detectable quantities, and RT-PCR remains the gold standard diagnostic of active infection.

Here is a frequently updated list of what diagnostic tests for COVID-19 are being developed worldwide; see which studies are marked with “(FDA)” to know which are available, or in the pipeline, for the US.

Molecular detection of 2019-nCoV in seven patients. Patient information can be found in Extended Data Tables 1, 2. Detection methods are described in the Methods. AS, anal swab; OS, oral swab. b, Dynamics of 2019-nCoV antibody levels in one patient who showed signs of disease on 23 December 2019 (ICU-06). OD ratio, optical density at 450–630 nm. The right and left y axes indicate ELISA OD ratios for IgM and IgG, respectively. c, Serological test of 2019-nCoV antibodies in five patients (Extended Data Table 2). The asterisk indicates data collected from patient ICU-06 on 10 January 2020. b, c, The cut-off was to 0.2 for the IgM analysis and to 0.3 for the IgG analysis, according to the levels of healthy controls.

(Zhou et al., Nature 2020)
Ancillary Studies

Workup for hospitalized patients

Given initial resource limitations and delays of PCR testing, hospitals around the world have been working off a clinical diagnosis of COVID-19 while awaiting definitive microbiological diagnosis. Many have shared laboratory and imaging findings of COVID-19 cases, helping physicians more precisely determine the pre-test probability of a given patient having COVID-19. This is a brief review of these findings for hospitalized patients; how exactly each component corresponds to the viral pathophysiology is still under investigation.

Laboratory diagnostics

Thought question:

Given what you know about laboratory values in viral infections in general, what would you predict the laboratory values to be in patients with COVID-19?

The hallmark laboratory findings in COVID-19 cases reported thus far is lymphocytopenia. In the Guan cohort of 1099 patients discussed above, these trends were seen: lymphocytopenia (83%), elevated CRP (61%), thrombocytopenia (36%), and leukopenia (33%). Less commonly, elevations were seen in ALT, AST, CK, and d-dimer (Guan et al., NEJM 2020). These laboratory trends are represented below in the typical fishbone format but REMEMBER - a patient need not have all or any of these laboratory values to be infected:

(Nick Mark, A Seattle intensivist’s one-pager on COVID-19)

A strong push has been made for identifying laboratory markers that can be used as clinical predictors of disease severity. Unsurprisingly, patients with more severe disease have been seen to have more prominent laboratory abnormalities across the board than those with nonsevere disease (Guan et al., NEJM 2020). Additionally, some inflammatory markers have been found to be significantly different between admitted patients that recover from COVID-19 compared to those who die. Specifically, those who died had higher levels of troponin, myoglobin, CRP, IL-6, ferritin, procalcitonin, LDH, creatine kinase, D-dimer, and lower lymphocyte counts, platelet counts and albumin (Ruan et al., Intensive Care Med 2020; Zhou et al., Lancet 2020). Larger scale studies will be needed to determine if these markers can accurately be used as clinical predictors of mortality and appropriate guides of resource allocation.
Temporal changes in laboratory markers from illness onset in patients hospitalised with COVID-19 (Zhou et al., Lancet 2020).

MGH recently published COVID-19 Management Guidelines recommending daily CBC, CMP, and CPK for all patients admitted with confirmed or suspected COVID-19 as well as risk stratification lab recommendations including d-dimer, ferritin/CRP/ESR, LDH, and troponin recommended q2-3 days or with clinical deterioration.
Imaging

**Thought question:**
What might be barriers to using imaging to routinely screen for COVID-19?

Studies have found that abnormal lung findings can be seen on chest CT for patients with COVID-19, even in asymptomatic cases (Shi et al., Lancet Inf Dis 2020). Despite this, concerns over resource allocation, infection control, and the limited diagnostic specificity of chest imaging for COVID-19 have resulted in recommendations against using chest radiographs or CT as a first-line form of diagnosis (American College of Radiology Position Statement, 3/11/20).

Chest CT may however be indicated for hospitalized patients with severe respiratory symptoms, and the most commonly seen findings for COVID-19 are described below.

**Thought questions:**
What imaging findings would you expect to see in a viral pneumonia?
Are the imaging findings for COVID-19 different from other viral pneumonias? How?

For a concise summary and multiple images of CT findings, please watch this [video](#).

The majority of imaging findings for COVID-19 are consistent with a viral pneumonia, with diffuse, bilateral involvement of the lung. The most common patterns seen are ground-glass opacities (GGOs), air-space consolidations, crazy paving (pattern of GGOs with inter/intra-lobular septal thickening), vascular enlargement, and traction bronchiectasis. Of note, GGOs, vascular thickening, and the peripheral distribution of these findings have been the most helpful in allowing radiologists to distinguish COVID-19 pneumonia from other viral pneumonias, but specificity remained quite variable across radiologists (24-100%) (Bai et al., Rad 2020). Imaging findings evolve over time, with abnormalities peaking at 10 days post symptom onset (Pan et al., Rad 2020), and fibrous stripes appearing with resolution (Pan et al., Eur Rad 2020). Imaging abnormalities, perhaps unsurprisingly, also correspond to disease severity, with dramatic increase in lung involvement correlating to rapid decline in patient prognosis (Shi et al., Lancet Inf Dis 2020).
Transverse thin-section CT scans in patients with COVID-19 pneumonia. (A) 56-year-old man, day 3 after symptom onset: focal ground-glass opacity associated with smooth interlobular and intralobular septal thickening in the right lower lobes. (B) 74-year-old woman, day 10 after symptom onset: bilateral, peripheral ground-glass opacity associated with smooth interlobular and intralobular septal thickening (crazy-paving pattern). (C) 61-year-old woman, day 20 after symptom onset: bilateral and peripheral predominant consolidation pattern with a round cystic change internally (arrow). (D) 63-year-old woman, day 17 after symptom onset: bilateral, peripheral mixed pattern associated with air bronchograms in both lower and upper lobes, with a small amount of pleural effusion (arrows). (Shi et al., Lancet Inf Dis 2020)

Lung ultrasound has also been used to evaluate critically ill COVID-19 patients, lung consolidation, B lines, septal thickening, and A lines during recovery (letter, Peng et al., Intensive Care Med 2020).
TREATMENT OF COVID-19

Clinical Course

The clinical course of COVID-19 is highly variable. For patients who progress to more serious disease, clinical outcomes include sepsis, respiratory failure, acute respiratory distress syndrome (ARDS), heart failure, coagulopathy, septic shock, acute cardiac injury, acute kidney injury, secondary infections, hypoproteinemia, and acidosis (Zhou et al., Lancet 2020). For information regarding some of the definitions of these clinical syndromes please reference the supplemental material, section clinical course. The role of cardiac injury in disease progression remains unclear at this time; however, acute cardiac injury and fast-onset heart failure with reduced ejection fraction (HFrEF) may be playing an important role in the death of certain patients.

In severe cases, the timeline of illness progression is also variable with time from onset of symptoms to severe manifestations (including pneumonia and ARDS) ranging from 8 days - 2 weeks. This progression is visually represented by a small cohort study of 41 admitted patients in China (Huang et al., Lancet 2020). While this is only representative of a small group of patients, it demonstrates the late worsening or possibly biphasic course seen in numerous cases thus far (MGH Grand Rounds 3/12/20; Holshue et al., NEJM 2020).

Overall case fatality rate (CFR) is difficult to discern because we are, for the most part, testing patients with more severe disease. You will hear the number 2% a lot. This primarily comes from the largest epidemiologic report out of China that showed an overall CFR of 2.3% (1023/44672) (Zhang et al, CCDC 2020). However, the numerator here is the number of deaths in this cohort (which is known), however the denominator is the number of CONFIRMED cases of COVID-19 in this cohort. There is currently no way -
particularly with how little surveillance screening is being performed - to determine the TRUE number of COVID-19 cases in this cohort or others like it, given that many patients are asymptomatic or mildly symptomatic and never present for care or testing. Therefore we hope this number is substantially lower than 2%. Of note, initial reports from Italy suggest a much higher CFR than seen in China, hovering around 8% (Lazzerini et al., Lancet 2020). It is possible that this too is due to the lack of surveillance testing but the high disparity between the numbers seen in China and the numbers seen in Italy warrant further attention as the US ramps up its response to the pandemic. An additional point from the Chinese data is that there was a large disparity between the CFR in Hubei province (2.9%), which include Wuhan, and outside of Hubei province (0.4%), suggesting that access to resources and healthcare capacity is likely playing a role in the lethality of COVID-19 and is a major driver behind the “flatten the curve” movement and recommendations (discussed in more detail in module 2) (Wu et al., JAMA 2020).

**Thought question:**
With such extensive variation in clinical severity, what criteria could we use to determine who to admit to the hospital? What about admission to the ICU?

**Triage Guidelines**

This is one example of a triaging guideline in a fever clinic in Wuhan, China (note that arbidol is an anti-influenza medication that is not used in the US; in the US, we may use oseltamivir instead). This diagram is not meant to be used to guide treatment decisions, but to give an example of a method that has been used in fever clinics, triaging healthcare institutions, in Wuhan.
The institution that you will be working at will have their own triage and treatment guidelines for emergency room providers and providers on the wards. As discussed in Imaging, the CDC and ACR currently do not support using chest x-ray or CT for diagnosis, due to poor specificity of these modalities (ACR, 2020).

If a patient with risk of exposure to COVID-19 or confirmed COVID-19 calls phone triage, presents to urgent care, or to the ED, first identify whether they have no symptoms, mild symptoms, or moderate-severe symptoms.

- Mildly ill patients have subjective or low-grade fever, dry cough, aches and pains, nasal congestion, headache, sore throat (Kirtz NPR 2020; WHO Department of Communication March 2020).
- Moderately ill patients have high-grade temperatures, shortness of breath/trouble breathing, chills, profound fatigue (Kirtz NPR 2020), and may have signs of pneumonia on imaging (China National Health Commission)
- Severely ill patients have symptoms including severe dyspnea, hypoxia, dehydration (Kirtz NPR 2020). Signs include RR>30, PaO2/FiO2<300, imaging concerning for ARDS (bilateral lung infiltrates within the last 1-2 days) (Casella et al. StatPearls March 2020)
- Critically ill patients will have frank respiratory failure, shock, and multiorgan failure (Casella et al. StatPearls March 2020)

The categorization of mild, moderate, and severe symptoms of COVID-19 definitions may have overlap. The morbidity of disease should be considered on a case-by-case basis in the setting of the patient’s comorbidities and well-being as a whole.

Per the China CDC report of 72,314 cases, 81% of patients were mild/moderately ill, 14% had severely ill, and 5% were critically ill. There were no reports of deaths for patients who were mildly, moderately, or severely ill; there was a case fatality rate of 49% in critically ill patients (Wu, McGoogan JAMA 2020).

Thought question:
What questions would a clinician ask over the phone to get a sense of a patient's dyspnea or hypoxia?

If mildly ill:
If a patient is calling on phone triage with only mild symptoms, try to assess if their symptoms can be managed with supportive care and self-isolation at home. A helpful tool for patients and providers for this determination is https://c19check.com/, an application made by providers at the Emory University School of Medicine.

Patients being evaluated in the ED with no symptoms or mild symptoms - who are not at risk of rapid decompensation and have reliable follow-up - should be discharged from the ED with a set of careful return precautions, direction to self-quarantine, instruction for caregivers, and instruction for how to practice supportive care:

- Return precautions would be instruction to call a provider or 911 if they have trouble breathing, worsening symptoms, high fevers, etc. The patient should let the clinic or the 911 operator know about their current symptoms and their prior exposure to COVID-19 over telephone.
- Self-quarantine includes avoiding going to public places or events, staying at home (preferably in a private room with a private bathroom), wearing a face mask, and cleaning doorknobs and other high touch household fixtures for at least 2 weeks after potential exposure; the decision to discontinue self-quarantine should be made with the help of healthcare providers (CDC). Per CDC guidelines, if patients had no symptoms but tested positive for COVID-19, they can end self-quarantine a week after their positive test - if they continue to be asymptomatic (CDC). For patients with mild symptoms, there are two strategies to discontinue self-quarantine, a test-based strategy (only realistic when enough testing resources are available) and non test-based strategy (which still prevents most secondary spread):
  ○ Test based strategy: All symptoms have resolved AND 2 confirmed negative results from nasopharyngeal swab molecular assays for COVID-19 - collected 24 hours or more apart (CDC)
  ○ Non test-based strategy: Patients with mild symptoms who were taking care of themselves at home can end self-quarantine 3 days after resolution of all symptoms AND if it has been over 1 week since they first started having symptoms (CDC)

Last updated 3/20/2020
Supportive care involves making sure the patient is eating and drinking well, and taking acetaminophen for comfort and fever-reduction (WHO Department of Communication March 2020).

- The effects of NSAIDS on COVID-19 disease severity remain controversial (BMJ News). While the WHO (WHO Twitter 3/18/2020) and the European Medicines Agency (EMA Press 3/18/2020) do not support the avoidance of ibuprofen/NSAIDs as there is no good evidence establishing a link between NSAIDs and worsening of COVID-19 severity. However, due to an abundance of caution, the easy availability of alternatives (ex. acetaminophen), and the theoretical risk that NSAIDs may pose (Fang et al. Lancet March 2020), many hospitals, including MGH, are avoiding NSAIDs until more definitive data emerges.

Patients with a high risk of exposure to COVID-19 or confirmed COVID-19, but with only mild symptoms, should be admitted if there is risk they will decompensate or do not have reliable follow-up. Other considerations for admission are if there are others at the patient’s residence who are at high risk of complications from COVID-19, if your patient doesn’t have access to necessary resources and personal protective equipment at home, and if your patient is unable to self-quarantine (CDC).

Thus far, there is very limited data for care for pregnant women with COVID-19 and for post-partum care. Routine ante-natal care continues to be encouraged. Individuals with high suspicion of COVID-19 or confirmed disease who are breastfeeding or having skin-to-skin contact with their infants should wear masks as appropriate and wash their hands before and after touching the baby. Please see the WHO clinical treatment guidelines for further details: WHO Dept of Communication March 2020.

**PPE Guidelines by the CDC**

When caring for patients with a URI of unspecified etiology or with suspected COVID-19 infection in the ED, providers are recommended to use droplet precautions (face mask or respirator), contact precautions, and eye protection. If these materials are disposable, they should ideally be discarded after the provider leaves the room. Patients should also be given droplet masks to wear throughout their visit if possible (CDC COVID-19 PPE guidelines).

Airborne precautions (ex. N95 Masks) should be used if providers are planning to intubate, administer HFNO or CPAP/BiPAP, or perform other procedures that may generate aerosols (CDC COVID-19 PPE guidelines).

If moderately, severely, or critically ill patients:

It is important to admit patients who are moderately, severely, or critically ill. The decision about whether or not to manage patients on the floor versus admit patients to the ICU is ideally dependent on a patient’s medical stability. ICU level care is needed for patients who are at high risk of decompensation, who need advanced ventilatory support, or who need support for 2+ systems (neurologic, renal, respiratory, circulatory). For patients with COVID-19, the patients at most risk for needing ICU level care are older patients and patients with comorbid conditions such as COPD, hypertension, cardiovascular disease, and diabetes mellitus (Smith, Nielsen BMJ 1999). The most likely need for ICU admission in this patient population is advanced respiratory support (Murthy et al. JAMA Insights 2020). Patients should be admitted if in or at risk for hypercarbic or hypoxic respiratory failure, are having or have had recent seizures, if they are at risk for losing
their airway, or if they are in shock, etc. It is also important to note whether your patient had previously noted wishes about not receiving ICU level care in an advanced directive (Smith, Nielsen BMJ 1999).

**Treatment**
The following measures are used for treatment of admitted patients who are moderately, severely, or critically ill:

- Hospitalization for routine monitoring of vitals
- Use National Early Warning Score (Smith et al. Resuscitation 2013; MDCALC), warning scores, to predict if a patient will decompensate
- Isolate the patient in a single private negative pressure in an airborne infection isolation room with HEPA filter if the patient is undergoing procedures that generate aerosols (sputum production, intubation, HFNO, BiPAP/CPAP, etc.)
  - If unable to provide airborne infection isolation room, be extremely cautious in giving patient airway devices that deliver 6L/min or more of oxygen (if not intubated) as this may generate aerosols (Cheung Lancet Respir Med 2020, Brewster et al. Preprint March 2020)
  - High flow nasal oxygen can give fraction of inspired oxygen (FiO2) up to 100% and reduces the need for intubation, but should be used with airborne precautions as it may produce aerosols (WHO Department of Communication March 2020)
  - BiPAP and CPAP may also generate aerosols and should be avoided if possible, or if used with caution if necessary (WFSA Coronavirus Guidance)
  - If a private room is not possible, keep 2+ feet distance between patients (Murthy et al. JAMA Insights 2020)
- If concomitant asthma or COPD, to give bronchodilators, use metered dose inhalers with a spacer instead of nebulizers due to risk of aerosolization (Wax, Christian Can J Anesth 2020)
  - If patient has severe asthma or COPD, consider epinephrine and early rapid sequence intubation
- Consult Infectious Disease and Pulmonology services early if not already involved
- Conservative fluid management - defined as net fluid balance of 0mL over the first 7 days - if patient has been diagnosed with ARDS and is not hypotensive or in shock (FACT trial NEJM 2006)
- If suspecting sepsis, give empiric antibiotics (for community acquired pneumonia vs healthcare associated pneumonia) within 1 hour of recognition of sepsis, and then work-up source of infection
- Consider oseltamivir in flu season or if you have a high suspicion that your patient has comorbid flu
- Strongly consider advanced ventilatory support/intubation if a patient is in respiratory failure (hypercarbic or hypoxic); for intubation specifics, please check out this link
- For summary review of ventilatory settings for ARDS treatment, please check out this link
- If patients have refractory hypoxemia even with advanced ventilatory support, consider extracorporeal membrane oxygenation (ECMO) if available (WHO Department of Communication March 2020)
- Treat shock with volume support and pressors

Please take a look at this link for up-to-date recommendations about how resources and space should be managed in ED and ICU settings: University of Washington
For examples of how experimental therapies are being used in clinic settings: click this link to see MGH treatment algorithms. Continue reading “Investigational Therapeutics” for information on the scientific basis for many of these experimental therapies.

Thought questions:
How do you personally balance the benefits vs risks of high flow nasal oxygen delivery? Would you use this treatment modality? In which situations?
What signs/symptoms/imaging findings would prompt you to think about giving empiric antibiotics?
INVESTIGATIONAL THERAPEUTICS & VACCINE DEVELOPMENT

This section will build off the fundamental SARS-CoV-2 virology and hypotheses of COVID-19 pathogenesis that you learned in the beginning of this module and explore the scientific basis of potential therapeutics and vaccines. For the most up-to-date information on clinical trials and approval of COVID-19 therapeutics and vaccine development see Module 3. As of 3/2/2020, here is a detailed guide of drugs and vaccines in development. As best as possible, we will maintain an update of in vitro and animal based studies of therapeutic effectiveness in this section.

Thought Questions:
Based on what you know about viral structure and pathogenesis, what kinds of drug targets do we already have on the market that could have efficacy in treating COVID-19?
Who will most benefit from investigational therapeutics? From a vaccine?

Investigational Therapeutics

There are currently no approved treatments or vaccines for any coronavirus in the US; this includes SARS & MERS. It is also important to note that corticosteroid treatment is not recommended for treating viral pneumonia, unless indicated for another medical reason (WHO 2020; Russell et al., The Lancet 2020).

Thought Question:
Given what you have learned previously about corticosteroids (a very nice visual review here!), why may they be detrimental to treatment of viral pneumonia? Under what circumstances may a patient with COVID-19 be considered for corticosteroid treatment?

A collection of case reports and/or series of cases from patients with SARS-CoV & MERS-CoV and more recent animal and in vitro studies indicate the following drugs as warranting further study. Please see Module 3 for the most updated clinical trials related to these drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Current prescribed use</th>
<th>Mechanism of Action</th>
<th>Prior evidence for use against related coronaviruses &amp; in vitro SARS-COV-2 work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>Novel antiviral drug developed for Ebola virus disease &amp; Marburg virus infections (Not currently used for Ebola or Marburg due to)</td>
<td>Nucleotide analog; causes premature termination of the viral strand made by the viral RNA-dependent RNA polymerase.</td>
<td>Both MERS-CoV and SARS-CoV-1 are inhibited by remdesivir in multiple in vitro systems. In mouse and non-human primate models, treatment led to significantly reduced lung viral load and improved respiratory function for both coronaviruses.</td>
</tr>
<tr>
<td>Medication</td>
<td>Clinical Activity</td>
<td>SARS-CoV-2 Activity</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Prevention of HIV</td>
<td>Activity against SARS-CoV-2 infectivity <em>in vitro</em> at micromolar levels</td>
<td>Treatment with Lopinavir/Ritonavir was associated with lower rates of death and ARDS <em>in retrospective studies of SARS-CoV-1</em>. However, in a recent open label RCT with 199 patients in Wuhan, China (enrollment from Jan 18 to Feb 3), lopinavir/ritonavir was not observed to have any benefit over standard of care (Cao et al., NEJM 2020). See module 3 for clinical trial updates.</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Catarrhal (respiratory tract mucous membrane inflammation)</td>
<td>Activity demonstrated against a broad array of RNA viruses <em>in vitro</em>.</td>
<td></td>
</tr>
<tr>
<td>Chloroquine / Hydroxychloroquine</td>
<td>Anti-malarials Hydroxychloroquine also used in treatment of AID such as SLE and RA due to its immunomodulatory effects</td>
<td>Not fully understood. Leading hypotheses include the inhibition of viral fusion to the cell membrane through pH modulation and limiting the glycosylation of cellular receptors on the viral membrane.</td>
<td>Since the 1960s, the antiviral activity of chloroquine has been noted in vitro. Cell culture inhibition of viral replication was noted for SARS-CoV-1 and MERS-CoV. Inhibits SARS-CoV-2 viral entry and viral replication <em>in vitro</em> at micromolar levels</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Immunosuppressive drug used to treat moderate/severe RA</td>
<td>Humanized monoclonal antibody against the interleukin-6 receptor. Its action against this receptor is thought to mitigate the profound inflammatory response observed in severely affected</td>
<td>No basic science research to support this approach presently. Interest in use generated solely from international human observational data during the SARS-CoV-2 outbreak. See module 3 for updates.</td>
</tr>
</tbody>
</table>
Passive Antibody Transfer

The role of our immune system is to develop “memory” against foreign pathogens so that once exposed a second time to said pathogens, neutralizing antibodies are used to quickly eradicate an impending infection. With this understanding, physicians and scientists have long argued that the transfusion of human convalescent sera (that which contains neutralizing antibodies from a recovered patient) could treat infection or be administered prophylactically to inhibit systemic infection (Casadevall and Scharff, Clin Infect Dis. 1995). In general, passive antibody transfer tends to be more effective for prophylaxis than for treating systemic infection, and therefore should be given shortly after symptom onset. While we don’t fully understand why temporality of administration affects efficacy, it is thought that smaller inoculums may be more manageable for neutralization than systemic infection or that the transferred antibodies modulate the receiver’s inflammatory response which is more easily done at earlier stages of infection.

*If interested in learning more about previous uses of convalescent sera for treatment of viral infections please read:*

- **Poliomyelitis:** Park, JAMA 1932
- **Measles:** Gallagher, Am J Pub Health Nat Health 1935; Park et al., JAMA 1926
- **Ebola:** Sahr et al., J. Infection 2017
- **Influenza:** Luke et al, AIM 2006; Hung et al., Clin Infect Dis. 2011;

Graphical representation from Casadevall and Pirofski, JCI 2020 of a potential convalescent sera therapy protocol in COVID-19. Serum collected from recovered COVID-19 patients that have high titers of neutralizing antibody would be administered prophylactically to high-risk individuals (elderly, patients with comorbid conditions, health care workers or individuals with known exposure) or to patients with severe disease to dampen severity of symptoms and mortality.

There is indeed a historical grounding for using passive antibody transfer in the treatment of related coronavirus infection. During the epidemics of SARS1 and MERS, high mortality and dearth of effective treatment options led to use of convalescent serum (Cheng et al., Eur J Clin Micro Infect Dis. 2005). In terms of using this kind of therapy for treating COVID-19, evidence is still lacking, but there is a great deal of interest. A recent study reported that sera collected from confirmed positive SARS-CoV-2 patients have the ability to
neutralize SARS-CoV-2 in an *in vitro* plaque assay ([Zhou et al., Nature 2020](nature2020)), which suggests this sera contains factors produced by a successfully mounted humoral response to SARS-CoV-2 antigens. There have been some reports that [convalescent plasma therapy has already begun](convalescentplasma), but for the most recent updates on the investigation or approval of this therapy in COVID-19 see [Module 3](module3).

**Vaccine Development**

*Thought Questions:*
Coronaviruses are a large family of viruses that cause the common cold and circulate widely - how do we find specific antigens to SARS-CoV-2 that will allow for specificity in protection against SARS-CoV-2? How do we balance the need to quickly develop and distribute a vaccine vs. the ethical considerations of testing the vaccine to make sure it is safe and effective? How will a potential vaccine be shared with the world and who should receive the vaccine first in instances where there is a limited supply (i.e. rationing)?

Vaccination holds the key to the effective prevention and potential eradication of various infectious diseases, and SARS-CoV-2 is no exception. Vaccines are used in healthy individuals to prevent the development of future illness, as well as to attenuate the duration and severity of symptoms in those who do develop illness in the future. **Most sources are indicating that a COVID-19 vaccine will not be ready for public use until at least 1 year from now** ([MGH Grand Rounds, 3/12/20](mgghandgrandrounds)).

Prior to a vaccine’s introduction on the market, scientists not only need to identify specific markers of the virus (antigens) to be incorporated into a vaccine used to stimulate the immune system, but will also need to undergo the entire clinical trial process to demonstrate that the vaccine is both safe and effective. (Review: [Vaccine Testing and Approval Process](vaccineapprovalprocess) and [video](video)).

- **Phase 1 trials** with small numbers of healthy patients will first strive to demonstrate that the vaccine is safe, void of adverse side effects and establish an acceptable dosage. This is especially important given that vaccines are given to healthy individuals, rather than sick individuals, and must reach a greater threshold for safety.
- **Phase 2 trials** enroll a larger group of individuals and aim to demonstrate the vaccine is effective in preventing the symptoms or disease under investigation. The subjects enrolled tend to be people that are considered to most benefit from a new treatment (i.e. elderly, persons with comorbid conditions).
- Upon successful completion of the prior stage, **phase 3 trials** enrolling even more patients will seek to show continued safety and efficacy.
- **Phase 3 trial**, the vaccine is generally approved and available to the general public, though **formal phase 4 trials** are *encouraged* (but not usually formally required) to assess for longer-term safety and efficacy.

While some clinical trials for COVID-19 vaccines are already underway in the US and abroad, what the medical and scientific community must consider is **which viral component will be used as a basis for developing immunity.**
The vaccine development for SARS-CoV-2 has evolved at a rapid pace and likely has been informed by knowledge from previous SARS and MERS vaccine development (see below figure). There are many different types of vaccines in the modern era, including whole pathogen vaccines which can be either 1) killed/inactivated or 2) live attenuated), subunit vaccines, mRNA vaccines, and DNA vaccines (Vaccine Types | NIH). The figure below illustrates some of the vaccines that had been previously developed for SARS and MERS, whose scientific basis are informing the approach to SARS-CoV-2 vaccine development.

<table>
<thead>
<tr>
<th>Vaccine platform</th>
<th>Immunogen</th>
<th>Phase</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
</table>
| DNA              | Full-length Spike, or S1  
• IM follow by electroporation | Phase I, II  
(NCT03721718) | • Rapid production  
• Easy design and manipulation  
• Induce both B and T cells responses | • Efficient delivery system required  
• Induce lower immune responses when compare with live vaccine |
| Viral vector     | Full-length Spike or S1  
• Vector used: ChAd or MVA | Phase I  
(NCT03399578, NCT03615911) | • Excellence in immune induction | • Varies inoculation routes may produce different immune responses  
• Possible Th12 bias |
| Subunit          | Full-length Spike, S1, RDB, nucleocapsid  
• Formulated with various adjuvants and/or fused with Fc | Preclinical | • High safety profile  
• Consistent production  
• Can induce cellular and humoral immune responses | • Need appropriate adjuvant,  
• Cost-effectiveness may vary |
| Virus-like particles | RDB, S or Co-expressing of S1, M, and E  
• Produced in baculovirus | Preclinical | • Multimeric antigen display  
• Preserve virus particle structure | • Require optimum assembly condition |
| Inactivated      | Whole virus  
• Inactivated by Formaldehyde or gamma irradiation | Preclinical | • Preserve virus particle structure  
• Rapid development  
• Excellence in neutralizing Ab induction  
• Can be formulated with various adjuvant | • Possible cause hypersensitivity  
• Possible Th2-bias |
| Live-attenuated virus | Mutant MERS-CoV and SARS-CoV or recombination with other live attenuated virus | Preclinical | • Excellence in induction of T and B cells responses  
• Site-directed mutagenesis can be tailor made | • Risk of reversion to a virulent strain  
• Cold chain required  
• Not suitable or sensitive population such as infants, immunocompromised or elderly individuals |
| DNA              | Full-length Spike, or S1  
• IM follow by electroporation | Phase I, II  
(NCT03721718) | • Rapid production  
• Easy design and manipulation  
• Induce both B and T cells responses | • Efficient delivery system required  
• Induce lower immune responses when compare with live vaccine |

ChAd: Chimpanzee adenovirus vector, MVA: Modified Vaccinia Ankara

Developed vaccines that have been in testing for SARS & MERS Prompatchara et al., APJAI 2020

Whole pathogen vaccines require the pathogen to be grown in the laboratory, where they can then either be killed with chemicals, heat, or radiation (to make a killed/inactivated vaccine) or weakened (to make a live attenuated vaccine), and then incorporated into the vaccine. Another approach is to incorporate part of the pathogen of interest’s genetic material into that of a harmless pathogen to create a “chimeric pathogen”, which can be used to stimulate the immune system.

Subunit vaccines utilize laboratory techniques to create the components (i.e. antigens) of the pathogen that best stimulate the immune system and incorporate these into a vaccine.
mRNA vaccines are developed by identifying the genetic sequence of the pathogen and then determining which sequences code important, unique components (antigens) of the pathogen. RNA for these genetic sequences is developed and then included in the vaccine. Once this RNA is introduced to a patient, the patient’s cells will use this RNA to make the corresponding pathogen’s protein, which will then stimulate the immune system. Another approach has been to target unique viral messenger RNAs as antigenic substrates for a host antibody response. These designs have been shown to have greater stability and protein translation efficiency which translates into a more robust immune response.

DNA vaccines work similarly to RNA vaccines. Instead of RNA, DNA is introduced in the vaccine to the patient. The patient’s cells use the DNA to make RNA, which then is used to make the corresponding pathogen’s protein and thus stimulate the immune system.

Nanoparticle vaccines utilize an understanding of synthetic biology to create nanoparticles out of proteins that are then studded with pathogenic components (antigens) for a pathogen. The idea is that while the underlying nanoparticle could stay consistent from vaccine to vaccine, the antigens could be switched out easily and interchangeably, allowing for rapid vaccine development. This could be especially important if the SARS-CoV-2 virus, as is feared, becomes a yearly illness like influenza. (To develop a coronavirus vaccine, synthetic biologists try to outdo nature)

Vaccines also commonly have adjuvants, which are used in order to increase the immune system’s response to a vaccine and thus develop a more effective immunity to a pathogen in the future. They have been used safely in vaccines for decades. (Adjuvants help vaccines work better. | Vaccine Safety)

In general, previous vaccine strategies for SARS & MERS have targeted the S protein, since it has been shown to play a role in inducing protective immunity by eliciting the production of neutralizing-antibodies and T-cell responses (Keng et al., J Virol. 2005; Zhou et al., J Virol. 2020; Bukreyev et al., Lancet 2004). Based on the function of this protein it is also an attractive target because immunity against this protein could block virus binding, impair membrane fusion or neutralize infection. However, the practical use of full-length S protein based vaccines is potentially hindered by the observation that they can induce immune mediated liver injury or enhanced infection following SARS-CoV rechallenge, despite successfully eliciting neutralizing antibody responses.

Summary

Knowledge on COVID-19 pathogenesis is emerging at a lightning pace, and the evidence-basis underpinning our diagnosis and treatment guidelines are constantly under review. We as medical students and global citizens are living and learning through a formative time. Now, more than ever, it is critical for the scientific and medical community to collaborate, to innovate, and to push the frontiers of our understanding.

GRAPHIC SUMMARY

● Review below, with highest quality available here.
We hope that this module highlighted the frontier of basic science and translational research on COVID-19. It provides a conceptual grounding on COVID-19 pathophysiology and how this relates to evolving diagnosis, treatment, and prevention efforts to prepare you for the impacts that this disease has on society, the government and our healthcare systems.

To continue in our COVID-19 curriculum, please click here: Module 2: Epidemiology Principles. Click here to return to the Overview.

We welcome your feedback on this module and on the curriculum overall. Please share it here.

COVID-19: Coronavirus Disease 2019
Harvard Medical School Module 1: From Bench to Bedside Graphic Summary

VIROLOGY
SARS-CoV-2 is a new strain belonging to the Coronaviridae family, which includes many pathogens such as COVID-19. This novel virus has been identified as the cause of the COVID-19 outbreak, and its identification has helped to inform strategies for disease control.

SARS-CoV-2 is classified as a class II pathogen, which requires biocontainment level 2 (BL2) to handle, as it is capable of causing moderate to severe disease in humans.

PATHOPHYSIOLOGY

Type 1 Pathophysiology
- Direct damage to respiratory epithelium
- Severe respiratory distress syndrome
- Acute respiratory distress syndrome
- Hypoxemia
- Acute respiratory distress syndrome

Type 2 Pathophysiology
- Immune-mediated injury
- Activation of innate immune system
- Overactivation of immune system
- Cytokine storm
- Organ failure

CLINICAL
Symptoms
- Fever
- Cough
- Fatigue
- Malaise
- Muscle aches
- Headache
- Sore throat
- Loss of taste or smell
- New loss of taste and smell

Risk-modifying factors
- Age
- Underlying medical conditions
- Comorbidities
- Obesity
- Smoking
- Chronic lung disease
- Pulmonary disease
- Obesity
- Hypertension
- Diabetes
- Heart disease
- Chronic kidney disease
- Cancer

Diagnosis
- Clinical presentation
- Laboratory testing
- Imaging studies
- Serology

Immunization

VACCINE
- mRNA vaccine
- DNA vaccine
- Viral vector vaccine
- Adenoviral vector vaccine
- Subunit vaccine
- Protein-based vaccine

TREATMENT
- Antiviral therapy
- Replication-inhibiting drugs
- Neutralizing antibodies
- Immune-modulating drugs
- Corticosteroids
- Anticoagulants
- Oxygen therapy
- Ventilator support
- ECMO

PREVENTION
- Universal vaccination
- Social distancing
- Mask-wearing
- Hand hygiene
- Contact tracing

INVESTIGATIONAL TREATMENTS
- Convalescent plasma
- Tocilizumab
- Remdesivir
- Hydroxychloroquine
- Convalescent plasma
- Anakinra
- Interleukin-6 receptor antagonist
- Bevacizumab
- Tocilizumab
- Sarilumab
- Lenalidomide
- Lenalidomide
- Hydroxychloroquine
- Convalescent plasma
- Convalescent plasma

We are committed to ensuring accuracy and up-to-date information. Please note that this information is current as of the last update on 3/20/2020.