Novel 2019 Coronavirus SARS-CoV-2 (COVID-19): An Updated Overview for Emergency Clinicians - 03-23-20

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About This Issue

The novel coronavirus, COVID-19, has quickly become a worldwide threat to health, travel, and commerce. It is essential for emergency clinicians to learn as much as possible about this dangerous outbreak, and to be able to separate fact from speculation. This overview analyzes the best information from the early research and offers valuable links to the most reliable and trustworthy resources to stay up-to-date. It contains links to the most reliable information sites that are likely to be updated on a daily basis and it will be your go-to resource to stay current on this fast-changing outbreak.

- How SARS-CoV-2 (COVID-19) differs in epidemiologic and demographic features from SARS-CoV-1 and MERS-CoV viruses
- Lessons learned from the experience of Dr. Andrea Duca, an emergency physician in Northern Italy, where the outbreak has devastated the healthcare system.
- The latest evidence on transmission and prevention through safe use of personal protection equipment
- New evidence and advice on SARS-CoV-2 testing and co-infection
- Helpful tips on imaging, and correlating CT and ultrasound
- Management options: antivirals, glucocorticoids, and novel treatments to manage cytokine storm
- Assessing airway management options: NIV, helmet CPAP, and filters
- Steps for rapid sequence intubation in the ED and managing disaster ventilation
- New information on managing pediatric and pregnant patients
- Is there a place for shared decision-making in times of pandemic?
- Where should I go for daily updates about Coronavirus COVID-19?

Key Points

- The current case fatality rate of COVID-19 is approximately 4%, though sampling error may be large. While this would make SARS-CoV-2 the least deadly of the 3 most pathogenic human coronaviruses, its relative virulence has shown an ability to overwhelm even relatively advanced health infrastructures, as noted by a current case fatality rate in Italy of 8.37% as of March 18, 2020.[1]
- Based on data from China, 29% of the confirmed COVID-19 patients are healthcare professionals, and 12% are hospitalized patients, suggesting an alarming 41% rate of nosocomial spread.[2]
- Recent data from the CDC suggests younger patients (20-44 years of age) are not as immune to significant disease as previously reported and have up to a 20% hospitalization rate; however, children aged < 18 years are generally spared from significant morbidity or mortality.
- Gastrointestinal (GI) symptoms are less frequently discussed, but new data suggest almost half of patients in a Chinese study had diarrhea, and the presence of GI symptoms was associated with worse disease outcome.
- In preparation for the arrival of patients suffering from COVID-19, emergency departments (EDs), hospitals, and healthcare systems should make immediate and necessary structural and process changes to prepare for high volumes of patients, primarily in respiratory distress, who will require mechanical support.

Introduction

Coronaviruses earn their name from the characteristic crown-like viral particles (virions) that dot their surface. This family of viruses infects a wide range of vertebrates, most notably mammals and birds, and are considered to be a major cause of viral respiratory infections worldwide.[3,4] With the recent detection of the 2019 novel coronavirus (SARS-CoV-2), and the resultant disease that has been given the name, coronavirus disease 2019 (COVID-19), there are now a total of 7 coronaviruses known to infect humans:

- Human coronavirus 229E (HCoV-229E)
- Human coronavirus OC43 (HCoV-OC43)
- Human coronavirus NL63 (HCoV-NL63)
- Human coronavirus HKU1
- Severe acute respiratory syndrome-related coronavirus (SARS-CoV-1)
- Middle East respiratory syndrome-related coronavirus (MERS-CoV)
- Novel coronavirus SARS-CoV-2[5]

Prior to the global outbreak of SARS-CoV-1 in 2003, HCoV-229E and HCoV-OC43 were the only coronaviruses known to infect humans. Following the SARS-CoV-1 outbreak, 5 additional coronaviruses have been discovered in humans, most recently the novel coronavirus SARS-CoV-2, believed to have originated in Wuhan, Hubei Province, China. SARS-CoV-1 and MERS-CoV are particularly pathogenic in humans

and are associated with high mortality. In this article, the epidemiology, pathophysiology, and management of COVID-19 are reviewed, with a focus on best practices and public health implications.

Critical Appraisal of the Literature

PubMed, ISI Web of Knowledge, and the Cochrane Database of Systematic Reviews resources from 2012 to 2020 were accessed using the keywords *emergency department, epidemic, pandemic, coronavirus, SARS-CoV-2,* and *COVID-19*. The websites of the United States Centers for Disease Control and Prevention (CDC); the World Health Organization (WHO); Japan's National Ministry of Health, Labor, and Welfare; and EMCrit were also accessed.

Epidemiology

As of March 22, 2020, there have been 328,275 confirmed cases of COVID-19 globally, with the majority of new cases now occurring outside of mainland China. There have been 14,366 confirmed deaths.[1] For up-to-date numbers on global confirmed cases/deaths from COVID-19, go to the Johns Hopkins University online tracker. At the time of this posting, confirmed cases span 169 countries across all continents except Antarctica, prompting the WHO to declare the SARS-CoV-2 infection a *pandemic*. Of the deaths, over half have now occurred outside of China, led by Italy (5476 deaths), and Iran (1685 deaths). The current global case fatality rate is 4.38%. With the outbreak of COVID-19 coinciding with the celebration of the Chinese Lunar New Year in late January 2020 and an associated approximate 15 million visits to Wuhan City, the efforts to contain the outbreak to mainland China were ultimately unsuccessful. Initial reports from affected patient populations in hospitals in China indicate that the majority of those infected with severe disease and poor outcomes (as measured by intensive care unit [ICU]-level care and mortality) tended to be patients with comorbid conditions such as hypertension, diabetes, obesity, asthma, chronic obstructive pulmonary disease, or advanced age.[2,6]

In epidemiology, the R_0 value (pronounced "R-naught") is known as the basic reproduction number and can be thought of as the expected number of cases generated directly by 1 case in a population, where all individuals are susceptible to infection. Early epidemiologic studies in the case of COVID-19 estimated an R_0 value of 2.2 (90% high density interval: 1.4-3.8), a value similar to SARS-CoV-1 and pandemic influenza, suggesting the potential for sustained human-to-human transmission and a global pandemic.[7] As will be discussed in more detail in the "Prevention" section, R_0 is a reflection of both virus behavior and human behavior, so with the correct societal and behavioral interventions, this R_0 value can be reduced.

With just mere months since the first case, the death toll from SARS-CoV-2 has far exceeded that of both MERS-CoV and SARS-CoV combined.[1] The true mortality rate is believed to be lower than the case fatality rate, due to selection bias, as only those with

symptomatology severe enough to prompt emergency evaluation and/or hospitalization are being tested for COVID-19.[8] Data from the *Diamond Princess* cruise ship outbreak provides a unique snapshot of the true mortality and symptomatology of the disease, given that everyone on board was tested, regardless of symptoms. Based on this data, unpublished analyses at the London School of Hygiene and Tropical Medicine have estimated an age-adjusted case fatality rate of 0.5%. This would still rank COVID-19 as deadlier than pandemic influenza, while maintaining a similar infectious profile.[9] Additionally, according to Japan's National Ministry of Health, Labor, and Welfare, 327 of the 697 people aboard the ship who tested positive for COVID-19 never showed symptoms, even up to a month after the initial positive test.[10]

COVID-19 Infection in Northern Italy: Lessons Learned

We are fortunate to provide a first-hand perspective to the COVID-19 crisis in Italy, which occurred a few weeks after Washington state's first reported case (January 21), and what epidemiologists have estimated is about 2 to 3 weeks ahead of the New York metropolitan area outbreak. Andrea Duca, MD is an emergency medicine physician and member of the Editorial Board of *Emergency Medicine Practice* based in Northern Italy, an area which bore the initial brunt of COVID-19. He reports that the rapid spread of SARS-CoV-2 overwhelmed most hospitals, which were unprepared to deal with the sudden influx of patients requiring ventilatory support. To date (as of March 18, 2020), Italy has a case fatality rate of 8.37%, which should serve as a warning to other healthcare systems around the world preparing to deal with patients with severe COVID-19 in the upcoming weeks. See **Table 1** for Dr. Andrea Duca's summary of lessons learned managing the SARS-CoV-2 outbreak in his ED in Bergamo, Italy. Additional data from that hospital are included in **Figures 1, 2, 3, and 4**. **Figure 1** presents a timeline of COVID-19 cases in the Lombardy region, February 20 to March 17, 2020; **Figure 2** lists the percentage of daily census admissions and discharges of COVID-19 patients, February 29 to March 10, 2020; **Figure 3** presents the total daily census admissions and discharges of COVID-19 patients; **Figure 4** presents a graphic display of the disposition of COVID-19 patients, February 29 to March 10, 2020.

Table 1. Lessons Learned from the Front Line of the COVID-19 Outbreak in Northern Italy: An Emergency Physician's Perspective, by Andrea Duca, MD

- Prepare to initially receive patients with upper airway symptoms, followed in the ensuing days by patients with persistent fever, and finally, patients with interstitial pneumonia. **The proportion of patients requiring admission increases day by day.** As of March 10, 2020, up to 60%-70% of patients presenting to the ED with suspected COVID-19 infection needed to be admitted, primarily for hypoxia. **See Figure 1** for a timeline of these trends and **Figure 2** for a graph of admission numbers by date.
- Be ready to adjust the spaces and the resources to the flow of incoming patients many times during the day, dividing "clean" flow from "dirty" flow. **It is fundamental to have leadership personnel on the floor to help manage the flow in the ED.**
- In the first days, the critically ill patients will be mostly older than 65 years, with comorbidities, followed by younger patients in the days/weeks after. Do not exhaust all of your resources with the first patients. **Patients will need to stay in the ICU for weeks.**
- **Patients come in waves, usually in late afternoon.** For every 100 patients coming to the ED, expect to have 5 with severe acute respiratory distress syndrome (ARDS), 10-20 with mild/moderate ARDS, and 40 patients needing oxygen to treat hypoxia.
- Do not rely on a negative nasal swab test. **If a patient looks like they have COVID-19 pneumonia, they usually end up having it.** Treat them as COVID-19 pneumonia, with isolation, and repeat the testing in 3 days. Every patient presenting with fever is a potential COVID-19 infection, even if they do not have respiratory symptoms.
- **Prepare in advance to have 10% of staff becoming ill.** Personal protection is hard to maintain during long shifts in a busy ED, but it is feasible, and constant vigilance is mandatory.
- Most admitted patients on respiratory support are PEEP responders. **Noninvasive ventilation is a powerful tool to buy some time until an ICU bed becomes available.** In Bergamo, our outbreak protocol is to start with helmet CPAP on all patients who remain hypoxic on maximal oxygen therapy and admit them to regular wards until an ICU bed is available. Intubation and invasive mechanical ventilation in the ED are reserved for patients not responsive to NIV. In our experience, mild to moderate ARDS responds well to helmet CPAP/NIV for the first several days. Expect severe ARDS to be responsive to NIV for only a short period of time.
- **In large health systems, strategize to designate one hospital to cohort COVID-19-positive patients** while keeping the other hospitals "clean."
- **Lung ultrasound is very helpful in evaluating patients on arrival.** It is more sensitive than chest x-ray, with a diffuse B-line pattern correlating to good response to PEEP.
- Tell all the patients with fever being sent home to return immediately if respiratory symptoms develop or worsen. Check home SpO_2, if possible. **In our experience, patients do not feel dyspneic until they become profoundly hypoxic.**
- **Prepare psychological support for the staff early.** You will need it.

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Figure 1. Timeline of COVID-19 Cases in Lombardy Region of Northern Italy

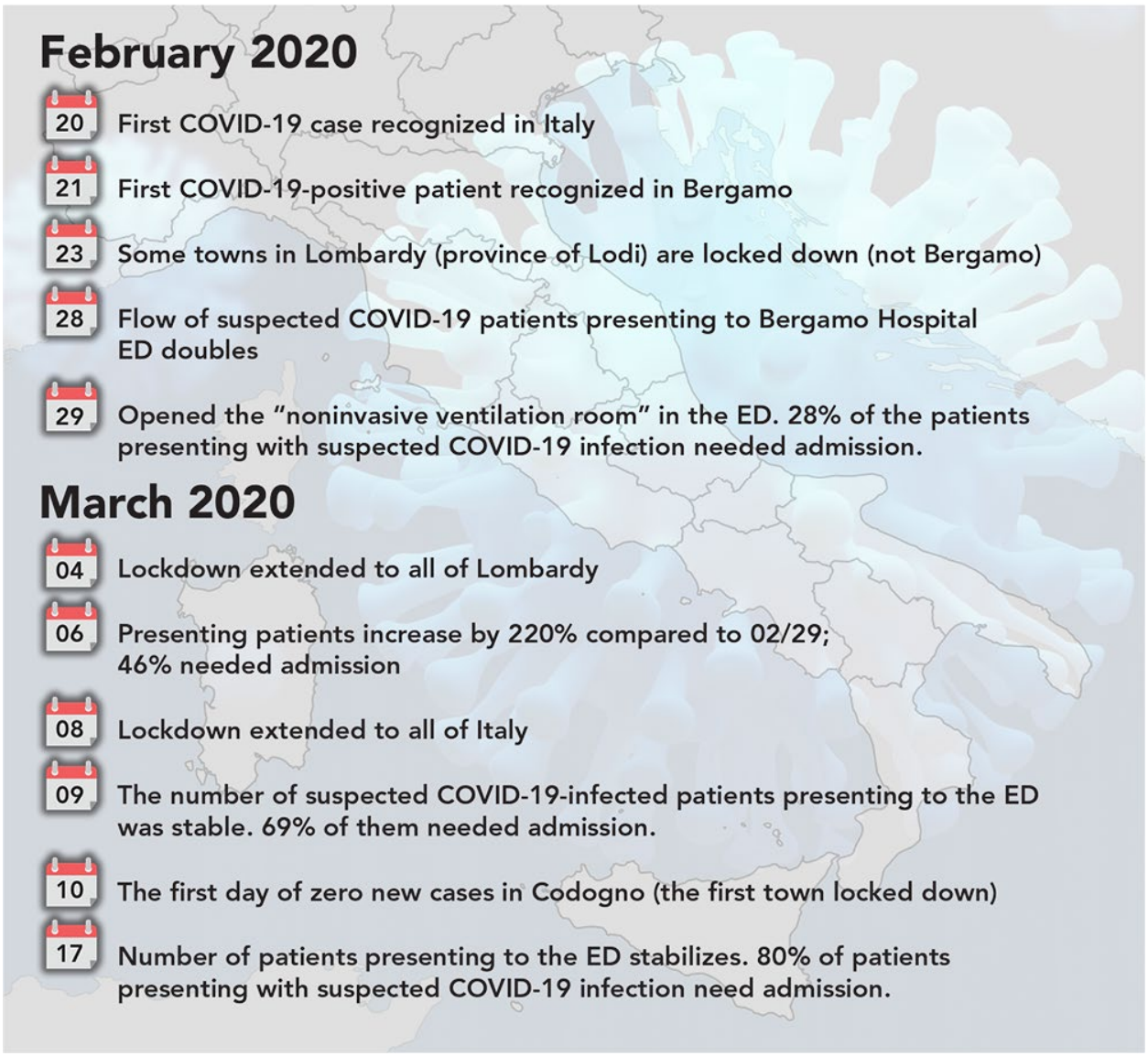

Figure 2. Percentage of Daily Census Admissions and Discharges of COVID-19 Patients in Bergamo, Italy

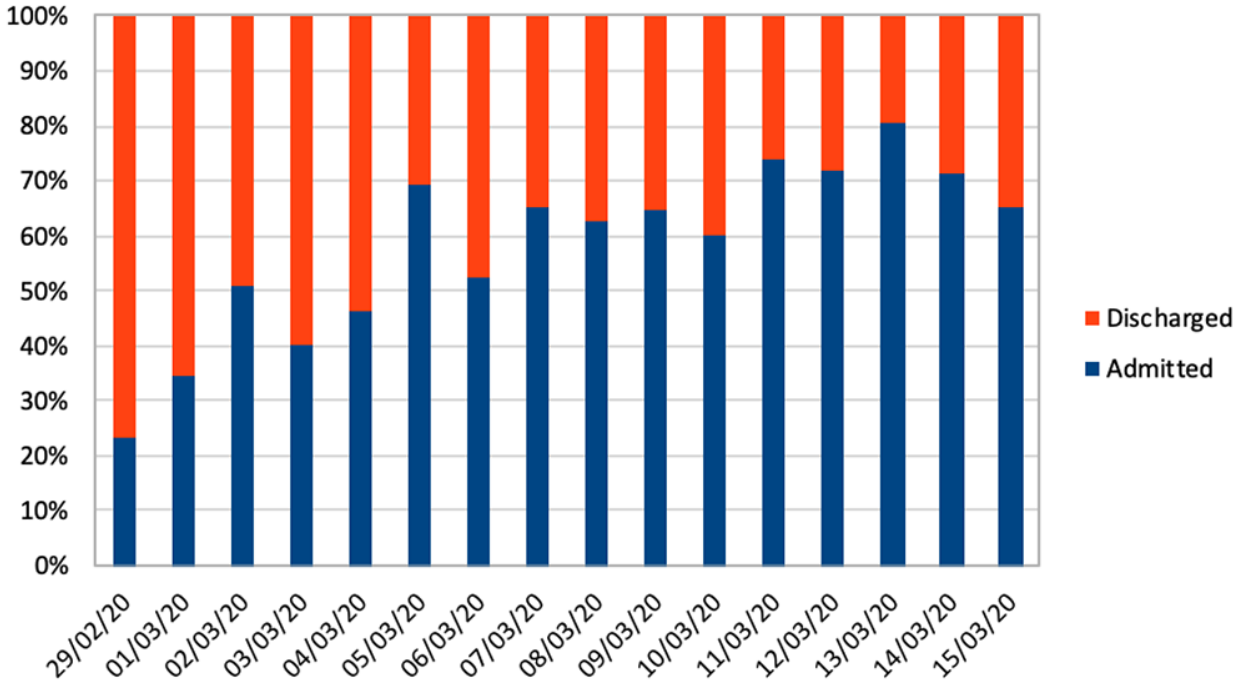

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Figure 3. Total Daily Census Admissions and Discharges of COVID-19 Patients in Bergamo, Italy

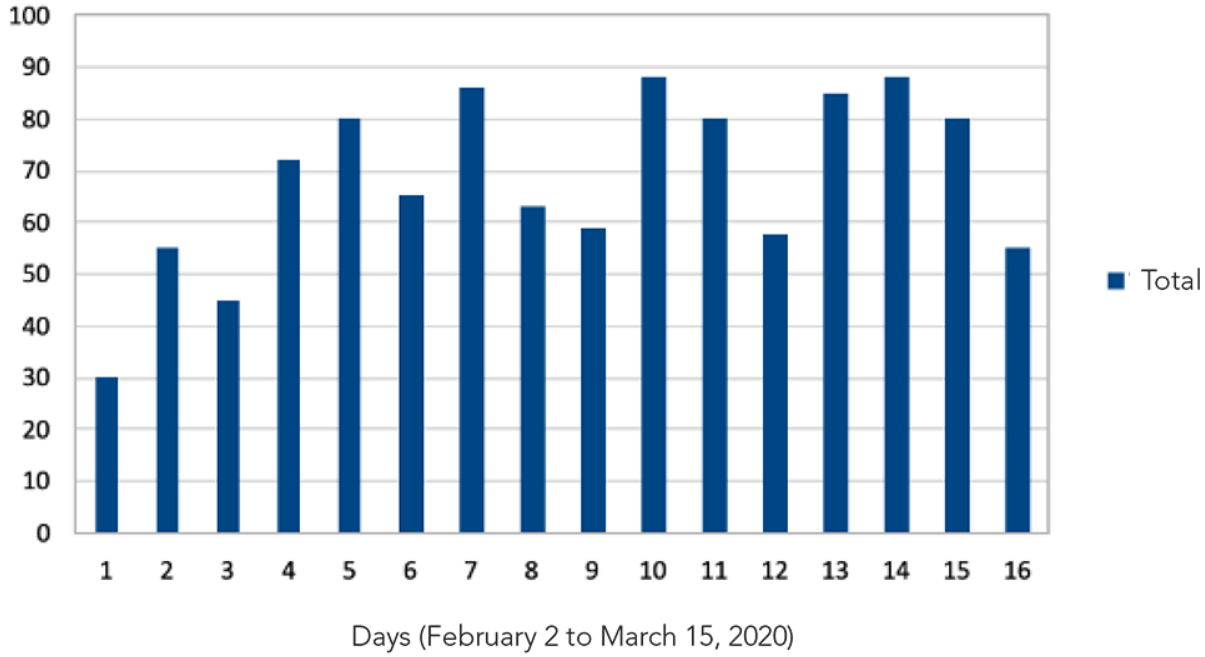

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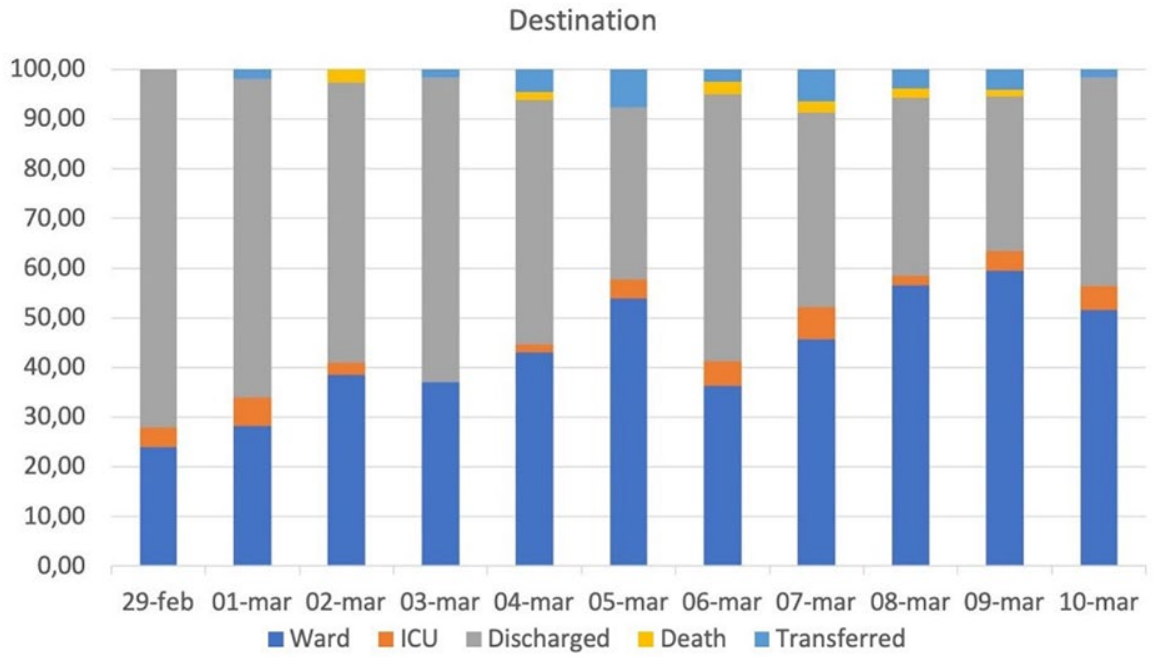
Figure 4. Day-by-Day Graphic Display of Disposition of COVID-19-Infected Patients in a Large Hospital in Bergamo, Italy



The y axis represents the percentage of total new presenting cases of suspected COVID-19 infection.

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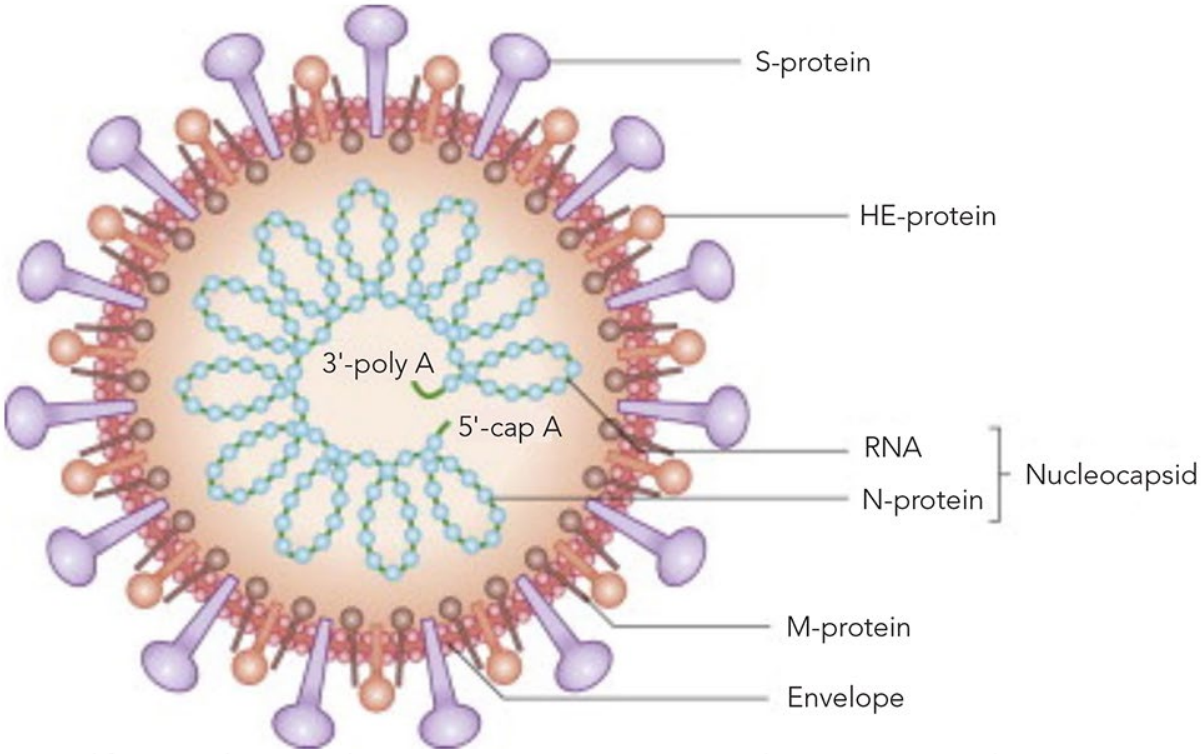
Virology

Coronaviruses are in the order Nidovirales, in the family Coronaviridae, and subfamily Orthocoronavirinae. Coronaviruses are enveloped with positive-sense single-stranded RNA, and possess the largest genome of all RNA viruses. Two-thirds of the coronavirus genome at the 5' terminus encodes viral proteins involved in transcribing viral RNA and replication, while one-third at the 3' terminus encodes viral structural and group-specific accessory proteins.[4] Our current understanding highlights 4 major proteins in coronaviruses: S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. These biomarkers play a central role not just in how we diagnose the disease, but how we will come to understand its pathogenicity profile, and ultimately any options for a vaccine and/or direct antiviral treatment targeted to dismantle the viral life cycle. **(See Figure 5.)**

Figure 5. Coronavirus With Major Proteins Labeled



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The SARS-CoV-1 and MERS-CoV viruses were both believed to have resulted from zoonotic spread from the bat population.[11] Naming the virus causing the current pandemic "SARS-CoV-2" is a result of its genetic similarity to the virus that caused the outbreak in 2003, which is now called "SARS-CoV-1." While coronaviruses likely evolved over thousands of years remaining confined to bat populations, intermediate mammalian hosts (such as civet cats in the case of SARS-CoV-1 and dromedary camels in the case of MERS-CoV) have been implicated and likely played a role in the ultimate transmission of these novel coronaviruses to humans.[12,13] The outbreak of COVID-19 is suspected to have originated in the Huanan Seafood Wholesale Market in Wuhan City; however, other researchers have suggested that this market may not be the original source of viral transmission to humans.[2,14] Bats are rare in markets in China, but they are hunted and sold directly to restaurants for food.[15]

Pathophysiology

Coronaviruses primarily infect the upper respiratory and gastrointestinal tracts of birds and mammals. The surface spike glycoprotein (S-protein) is a key factor in the virulence of coronaviruses, as it enables it to attach to host cells. MERS-CoV has been shown to

bind to dipeptidyl-peptidase 4 (DPP4), a protein that has been conserved across species known to harbor this strain of coronavirus. While most respiratory viruses infect ciliated cells, DPP4 is expressed in nonciliated cells in human airways, which is believed to be an important factor in its zoonotic transmission and high case fatality rate.[16] In SARS-CoV-1, human angiotensin-converting enzyme 2 (ACE2) was the primary cellular receptor to which the virus attached, and is believed to have played a role in the ability of SARS-CoV-1 to produce infections of both the upper and lower respiratory tracts, contributing to its infectivity and lethality.[17]

Previous studies have suggested that immunopathogenesis, also referred to as "cytokine storm," leads to the deterioration of patients dealing with various respiratory viruses, including SARS-CoV-1 and avian influenza.[18,19] A number of studies support the theory that the rapid deterioration of COVID-19 patients is driven by immunopathogenesis, whereby release of inflammatory markers initiates a positive feedback loop that leads to ARDS, multiorgan failure, and death.[20] A cohort of 41 laboratory-confirmed COVID-19 patients in China found that ICU patients had significantly higher levels of inflammatory markers (IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1, and TNF-alpha) than non-ICU patients.[21] A recent study conducted in China provides a detailed immunopathology report on SARS-CoV-2, suggesting patients with severe COVID-19 express an "…excessive activated immune response…by pathogenic Th1 cells and inflammatory monocytes," findings that are additionally supported by immunohistochemical analysis of postmortem lung biopsies of COVID-19 patients.[22,23] A growing body of literature suggests secondary or virus-induced hemophagocytic lymphohistiocytosis (HLH), a hyperinflammatory syndrome, to be the underlying cause of deterioration in these patients. This disease process carries a similar cytokine profile to patients with COVID-19, and includes cardinal clinical features of unremitting fever, cytopenias, hyperferritinemia, and pulmonary involvement.[24,25] Immunomodulatory therapies that are being considered in the treatment of COVID-19 will be discussed in the "Management" section.

SARS-CoV-2 enters type 2 pneumocytes in humans via the same ACE2 receptor as SARS-CoV-1.[26] A multicenter retrospective cohort study examining risk factors associated with inhospital death found hypertension to be the most common comorbidity in COVID-19-diagnosed patients requiring admission (30%), followed by diabetes (19%).[27]

Much has been made in recent weeks of the potential link between the commonly used antihypertensives, ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), and elevated risk for severe COVID-19 infection based on the binding of SARS-CoV-2 on ACE2 receptors. At this time, the official recommendations by the European Society of Cardiology, the American College of Cardiology, American Heart Failure Society, and the Heart Failure Society of America collectively state that patients on ACEIs and ARBs should continue their medications. The European Society of Cardiology stated, "there is no clinical or scientific evidence to suggest that treatment with ACEIs and ARBs should be discontinued because of the COVID-19 infection,"[28] and the joint HFSA/ACC/AHA

statement noted, "there are no experimental or clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients using ACEI or ARB medications."[29]

Similar concerns over the use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, have been raised based on postulated interactions with SARS-CoV-2 binding to ACE2 receptors. There is currently no scientific evidence to suggest that taking NSAIDs worsens COVID-19. Clearly, prospective multicenter trials should be conducted to investigate this issue further. A full discussion of the theoretical benefits and harms to patients on these medications can be found in "nephjc"

Prevention ("Flattening the Curve")

Much can be learned from the change in the dynamics of transmission following implementation of strict travel restrictions and quarantining measures in mainland China. A mathematical modeling study published in *The Lancet* estimated that the median daily reproduction number (R_t) in Wuhan declined from 2.35 (95% confidence interval [CI], 1.15–4.77) 1 week before travel restrictions were introduced on January 23, 2020, to 1.05 (0.41–2.39) 1 week after.[30] The effectiveness of broad governmental and societal interventions has been documented by multiple data-driven analyses, and should prompt all governments to act accordingly to prioritize early detection, isolation, and treatment; to supply adequate medical supplies; and to establish a system in which patients are admitted to designated hospitals with a comprehensive therapeutic strategy.[30,31] Utilizing a stochastic transmission model parameterized to the COVID-19 outbreak, Hellewell et al concluded that "highly effective contact tracing and case isolation is enough to control a new outbreak of COVID-19 within 3 months."[32]

A study published on March 16, 2020 by the Imperial College of London and WHO compared 2 fundamental policy strategies to reduce the rate of spread of SARS-CoV-2: "(a) mitigation, which focuses on slowing but not necessarily stopping epidemic spread – reducing peak healthcare demand while protecting those most at risk of severe disease from infection, and (b) suppression, which aims to reverse epidemic growth, reducing case numbers to low levels and maintaining that situation indefinitely." The study found that "…optimal mitigation policies (combining home isolation of suspect cases, home quarantine of those living in the same household as suspect cases, and social distancing of the elderly and others at most risk of severe disease) might reduce peak healthcare demand by two-thirds, and deaths by half. However, the resulting mitigated epidemic would still result in hundreds of thousands of deaths and health systems (most notably intensive care units) being overwhelmed."[33] This explains and lends support to the aggressive measures taken by countries in recent days to battle the spread of the SARS-CoV-2 pandemic.

Reports from Italy suggest that up to 20% of healthcare professionals dealing with COVID-19 patients became infected with the virus, with some reported deaths.[34] Losing healthcare workers to illness at a time when they are needed the most can be the tipping point for healthcare systems that are already stretched to the breaking point by

high volumes of sick patients. Recognition of the crisis in Italy underscores the importance of strictly enforcing preventive measures to all healthcare professionals. This has been accomplished in some systems by assigning one person to monitor compliance in the ED at all times.

Based on the transmission specifications of coronaviruses as a class, and documented transmission patterns of the SARS-CoV-1 and MERS-CoV outbreaks, the transmission of SARS-CoV-2 is presumed to be primarily through droplets and fomites, although viral particles have also been found in feces of seropositive patients. A preprint article published in *The New England Journal of Medicine* by researchers at the United States National Institutes of Health, Princeton University, and the University of California Los Angeles, found estimated half-lives for SARS-CoV-2 virus on various surfaces as follows: 1.1 hours in aerosols, 0.77 hours on copper, 3.46 hours on cardboard, 5.46 hours on steel, and 6.81 hours on plastic. These results indicated a plausible likelihood of aerosol and fomite transmission of SARS-CoV-2, and lend credence to its reported high rate of spread.[35]

Both the WHO and CDC guidelines for infection control emphasize the importance of strict hand hygiene in curtailing SARS-CoV-2 transmission. This stems from the uncertainty surrounding the transmission vectors aboard the quarantined *Diamond Princess* cruise ship off the coastal waters of Japan, as well as increasing reports from around the world of COVID-19 appearing in people who had not had direct contact with known or suspected carrier(s) or traveler(s) to an endemic area.[36,37] Given the reports from the Chinese CDC of SARS-CoV-2 virus being found in the feces of seropositive patients, the likelihood of fecal-oral and, hence, hand transmission is very high.[38] Healthcare professionals and patients should follow standard hand-washing techniques: wash hands with soap and water for at least 20 seconds, especially after going to the bathroom; before and after eating; and after blowing the nose, coughing, or sneezing. If soap and water are not available, one should use an alcohol-based sanitizer with at least 60% alcohol.[5]

Additional guidelines for those with close contacts and suspicious exposures include "strong recommendations" for immediate medical attention, an observation period of 14 days, wearing of a facemask if coughing or with URI symptoms, prioritizing private transportation over public, prenotification of the hospital (or clinic) prior to patient arrival, and cleansing of the transport vehicle with 500 mg/L chlorine-containing disinfectant, with open ventilation.[39] Note that the recommended observation period may soon be modified, given recent case reports and studies suggesting incubation periods from 0 to 24 days.[40,41]

Given the recent shortages of N95 respirator masks and other PPE, there is an increased need to follow current recommendations to account for changing availability of these necessary supplies. These can and should be followed in real time using the links supplied in Table 3. Additionally, recent considerations include recommendations to designate entire units within the facility with dedicated healthcare personnel to care

for known or suspected COVID-19 patients, along with need for airborne infection isolation rooms (AIIRs).[2]

Use of Personal Protective Equipment

Doffing of personal protective equipment (PPE) is often the highest-risk procedure during the patient-physician interaction, in terms of spread of SARS-CoV-2. Below is a simple step-by-step approach put together by emergency clinicians at EMCrit on the proper doffing of PPE after evaluation of a suspected or confirmed COVID-19 patient.[42] **(See Table 2.)**

Table 2. Procedure for Safe Doffing of Personal Protective Equipment

Inside the Patient Room (or in an anteroom)

1. Clean gloves with alcohol-based hand sanitizer
2. Remove gown and gloves
   a. Pull the gown forward to tear the gown away from the body
   b. Roll gown inside out and away from the body, bending forward, creating a "glove/gown ball"
3. Clean hands with alcohol-based hand sanitizer
4. Remove face shield
   a. Don't touch the front of the shield, which may be dirty
   b. Remove by touching the band of the face shield
5. Clean hands with alcohol-based hand sanitizer

Outside the Patient Room

1. Remove N95/surgical mask using the straps to pull the mask away from your face
   b. Front of the mask may be contaminated – do not touch this
   c. Avoid touching your face with hands or straps of the mask
2. Clean hands with alcohol-based hand sanitizer

A video of the correct procedures for donning and doffing PPE is available in YouTube at https://youtu.be/0YUOGvtyNNI

Evaluation and Diagnosis in the Emergency Department

Experience from Bergamo, in the region of Lombardia in Northern Italy, provides a model of response that may help other systems prepare. That region's EDs encountered an overwhelming volume of patients in severe respiratory distress over short periods of time which required immediate adjustments to flow and throughput. A summary of these changes and recommendations are listed in **Table 1**. Of note, much of the data are estimates based on preliminary data collection.

ED staff must maintain a high index of suspicion when evaluating all patients, but especially those with fever, cough, dyspnea, or signs of a respiratory illness. The CDC had initially focused their travel warnings and epidemiological risks on those with recent

travel or contact with a traveler to Wuhan City, Hubei province, China; however, having reached pandemic status with significant community spread, the connection to China is no longer relevant as a criterion to rule out SARS-CoV-2 infection.

Clinical Characteristics

In late January 2020, the first data detailing the clinical features, course, and prognosis from infection with SARS-CoV-2 relative to the previous 2 deadly coronavirus outbreaks (MERS-CoV and SARS-CoV-1) were published in *The Lancet.*[21,43] Since then, a multicenter retrospective cohort analysis of 1099 patients was published in *The New England Journal of Medicine,* which provides an updated glimpse of demographic and clinical characteristics of COVID-19.[41] **Table 3** differentiates symptomatology in patients with severe versus nonsevere disease, as defined by the American Thoracic Society guidelines for community-acquired pneumonia.[44] Patients with severe disease were older than those with nonsevere disease by a median of 7 years, and had much higher rates of comorbidity, namely hypertension (23.7% vs 13.4%, respectively) and diabetes (16.2% vs 5.7%, respectively). This table and article can be viewed in The New England Journal of Medicine. **Table 3** summarizes the early characteristics of SARS-CoV-2 compared to MERS-CoV and SARS-CoV-1.

Table 3. Early Demographic and Clinical Characteristics of SARS-CoV-2 Relative to Outbreaks of Previously Novel Coronaviruses, MERS-CoV and SARS-CoV-1[43]

Clinical Characteristics	SARS-CoV-2	MERS-CoV	SARS-CoV-1
Epidemiologic Statistics[a,b]			
Cases	328,275	2494	8096
Deaths	14,366	858	744
Case fatality	4.38%	37%	10%
Demographic Statistics[b,c]			
Date	December 2019	June 2012	November 2002
Location of first detection	Wuhan, China	Jeddah, Saudi Arabia	Guangdong, China
Median age, years	51 (IQR 35-58)	56 (range 14-94)	40 (range 1-91)
Male:female ratio	1.4:1	3.3:1	1:1.25
Symptoms (%)[b,c]			
Fever	44*	98	99-100
Dry cough	68	47	29-75
Dyspnea	19	72	40-42
Sore Throat	15	21	13-25
Diarrhea	3.8	26	20-25
Oxygen Requirements[b,d] (%)			
Oxygen therapy	82	--	--
Invasive ventilatory support	3.0	80	14-20
Non-invasive mechanical ventilation	30	--	--
Nasal cannula	49	--	--

[a]Epidemiologic statistics on SARS-CoV-2 as of March 15, 2020 based on Johns Hopkins CSSE global tracker.[1]

[b]All demographic and symptom statistics for MERS-CoV and SARS-CoV-1 were derived from referenced table by Chaolin Huang, et al.[21]

[c]Demographic and symptom statistics for SARS-CoV-2 are based on a multicenter retrospective review of 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020 as reported by Wei-jie Guan, et al.[41] Data are n, or n% unless otherwise stated.

[d]Oxygen requirements based on a retrospective cohort study involving 201 patients with confirmed COVID-19 pneumonia, published March 13, 2020.[48]

*While 44% of patients had fever on presentation, 89% of these patients ultimately recorded a documented fever during their hospitalization.

On March 18, 2020 the *American Journal of Gastroenterology* published a new study from the Wuhan Medical Treatment Expert Group for COVID-19 in China revealing that GI symptoms, such as diarrhea, are common in SARS-CoV-2 infection.[46] In 204 patients confirmed to have SARS-CoV-2, 99 (48.5%) had GI symptoms, and 7 of the patients with GI symptoms had no respiratory symptoms whatsoever. This is clearly a departure from the purely respiratory disease current guidance has provided, but consistent with the observed fecal-oral transmission patterns noted in earlier cited Chinese studies. Furthermore, the prognosis of patients with GI symptoms was worse than for those with purely respiratory symptoms. They found that patients without digestive symptoms were more likely to be cured and discharged than patients with digestive symptoms (60% vs 34.3%). The authors failed to ascertain the etiology of the mortality and morbidity difference between COVID-19, and recommend further studies.[46]

It should be noted that in the initial data from Bergamo, Italy described by Dr. Andrea Duca, there is a reported association of obesity with disease severity and need for intubation/critical care. From the same data, the rates of patients needing NIV or intubation in the ED are similar to data from Wu et al,[45] accounting for up to 31% of suspected COVID-19 patients admitted to the hospital. It is still too early to know how many patients who were started on NIV in the ED will be converted to invasive ventilation during the hospital stay and how many on oxygen will deteriorate and need to be ventilated. These data are still being collected and analyzed, and will soon be available for analysis and publication.

SARS CoV-2 Testing

Within 1 month of initial reports detailing the SARS-CoV-2 outbreak, the CDC developed a real-time reverse transcription-polymerase chain reaction (rRT-PCR) test to detect SARS-CoV-2. While diagnostic testing in the United States was available initially only through the CDC, this assay is now being made available at the state level with the use of the International Reagent Resource (IRR). The IRR was initially established by the CDC for the study and detection of influenza, but it has been expanded to include newly discovered influenza and coronaviruses.[47,48] It should be noted that widely available respiratory viral panels test only for the earlier forms of human coronavirus, namely human coronaviruses 229E, NL63, OC43, and HKU1.[49] The SARS-CoV-1, MERS-CoV, and SARS-CoV-2 strains require specialized assays that are becoming increasingly available. Unfortunately, the initial United States testing efforts were hampered by faulty initial test kits (due to problems with the reagent), and as a result, there was a lack of testing available for the majority of the country. **Table 4** summarizes the current recommendations for SARS-CoV-2 testing.

Table 4. Recommendations for SARS-CoV-2 Testing

1. **Hospitalized patients who have signs and symptoms compatible with COVID-19 should be tested in order to inform decisions related to infection control.**
   - As seen in **Table 1**, if patients clinically appear to have COVID-19 pneumonia, regardless of the x-ray findings, they most likely have it. Isolate and retest in 3 days if the first test is negative, given the high rate of false-negatives.[50]
   - Among patients with suspected COVID-19 and a negative initial PCR, repeat PCR was positive in 15/64 patients (23%). This suggests a PCR sensitivity of < 80%.[50] Conversion from negative to positive PCR seemed to take a period of days, with CT scan often showing evidence of disease well before PCR positivity.[50] See the "Lung Ultrasound" section for discussion of the early sensitivity of lung ultrasound and the utility of ultrasound over CT scan to guide management.
2. **High-risk symptomatic individuals should contact their physician early in the course of even mild illness.** Groups at higher risk for poor outcomes include older adults and individuals with chronic medical conditions and/or an immunocompromised state. Risk factors include diabetes, heart disease, chronic lung disease, chronic kidney disease, and receiving immunosuppressive medications.

www.ebmedicine.net

Previous Testing Recommendations

In what has become a controversial policy reversal as the outbreak increases in the United States, there is a significant departure from previous guidance of testing any persons, including healthcare personnel who have had close contact with a suspected or laboratory-confirmed COVID-19 patient, or who have a history of travel from endemic areas within 14 days of their symptom onset. At the time of this publication, the current recommendation is to **not** test the asymptomatic healthcare workers who have known exposures, or other asymptomatic individuals with concerning exposures and/or travel history. There is also a pedaling back of recommendations to test any persons who do not need to be admitted to the hospital. It is unclear at this point whether these recommendations will change again.

There are additional epidemiologic factors that may also help guide decisions about SARS-CoV-2 testing. Documentation of COVID-19 in a locality with known community transmission may assist with the epidemiologic risk assessment to guide testing decisions. However, the inability of many locales and hospitals to test all persons has led to a rescinding of this recommendation. Given the increasing concern about the availability and reliability of SARS-CoV-2 testing, there is varying guidance provided at the federal, state, and local levels. Nonetheless, when clinicians decide to test, they should recall that in cases of high suspicion and based on early research in China (as well as reported by Duca in Italy, two negative tests repeated at least 24 hours apart (3 days in Italy), are needed to exclude COVID-19 as a diagnosis.[51]

In the initial onset of SARS-CoV-2 outbreak in the United States, many clinicians were encouraged to test for other causes of respiratory illness (eg, influenza), based on recommendations from their infectious disease and infection prevention services.

However, there has been ongoing debate regarding the testing and evaluation for COVID-19 in relation to co-infections with other viruses.

After an exhaustive search of the literature, interviews with several infectious disease physicians, consultation of several national and international forums dedicated to both emergency medicine and COVID-19, we were able to find only a single non-peer reviewed Chinese study of 8274 specimens collected and analyzed for SARS-CoV-2 and other viral species. (Note that the publisher states, “This article is a preprint and has not been peer reviewed. It reports medical research that has yet to be evaluated and so should not be used to guide clinical practice.”) In this study, they found that 5.8% of COVID-19 patients had co-infections with other viruses, and that 18.4% of other (non-SARS-CoV-2) infections had other co-infectants.[52] The authors acknowledged the unreliability of their tests for both SARS-CoV-2 and other viruses, which may underreport the actual co-infection rate. Furthermore, in some preliminary data reported by Stanford Medicine Data scientists, and immediately available to the public online at the behest of the California Department of Public Health, researchers found that in the 49 positive SARS-CoV-2 results, 11 (22.4%) also had co-infection with another virus.[53] We anticipate that a large, validated study will help to shed further light on the rate of co-infection with SARS-CoV-2. In the meantime, we must recommend that clinicians maintain a high index of suspicion for SARS-CoV-2, regardless of the presence of other viruses.

Given this information, emergency clinicians should re-emphasize to the lay public what we already know of viral respiratory infections: that seeking treatment in a hospital setting for mild symptoms, fever, mild diarrhea, or cough alone likely carries with it more risk than benefit, both to themselves and to vulnerable patients around them. Patients experiencing severe symptoms such as difficulty breathing, high fever (>39°C), and an inability to tolerate oral hydration should seek emergency evaluation. For those who are concerned about their symptoms or concerned about spreading the infection to vulnerable family members, care should be taken to practice social distancing, self-quarantining, and utilization of telehealth and drive-through screening clinics to receive medical evaluation and testing (if warranted) while minimizing risk of infectious spread. Though beyond the scope of this review, further discussions regarding institutional and departmental policies that weigh the need to protect the health of medical staff and care for patients versus the need to minimize nosocomial spread from asymptomatic healthcare workers who may infect patients, will need to continue.

As illustrated in Table 1 of a recent study published in *The Lancet*, univariate analyses of the following patient characteristics and laboratory markers were associated with increased mortality: increased age, lymphopenia, leukocytosis, and elevations in ALT, lactate dehydrogenase, high-sensitivity cardiac troponin I, creatine kinase, D-dimer, serum ferritin, IL-6, prothrombin time, creatinine, and procalcitonin.[27] Multivariate regression models showed increasing odds of in-hospital death associated with older age (odds ratio [OR], 1.10; 95% CI,1.03-1.17 per year increase, $P = .0043$), higher sequential organ failure assessment (SOFA) score (5.65, 2.61-12.23; $P < .0001$), and

D-dimer > 1 mcg/mL (18.42, 2.64–128.55; *P* = .0033) on admission.[27] This table can be found at The Lancet

A recently published meta-analysis on procalcitonin in COVID-19 patients suggests that procalcitonin levels should remain in the reference range in patients with noncomplicated COVID-19, and that an elevation in procalcitonin may reflect bacterial co-infection in patients developing a severe form of COVID-19.[54] A meta-analysis of platelet counts in COVID-19 patients found that thrombocytopenia is associated with increased risk of severe disease, and that a substantial decrease in platelet count should serve as a clinical indicator of worsening illness in patients hospitalized with COVID-19.[55] See **Table 5** for laboratory markers correlating with disease severity and clinical management for patients with COVID-19 pneumonia.

Table 5. Laboratory Markers Correlating With Disease Severity and Clinical Management for Patients With COVID-19 Pneumonia

Laboratory Test	Abnormality Seen in Patients With COVID-19[27]
Complete blood cell count	Lymphocytopenia, thrombocytopenia[55] associated with severe disease
Complete metabolic panel	Mild to moderate elevations in AST/ALT, creatinine associated with severe disease[27]
Coagulation markers	Mildly elevated prothrombin time associated with severe disease, significant elevation in D-dimer predictor of mortality
Lactate dehydrogenase	Significant elevation associated with severe disease
Creatine phosphokinase	Elevation associated with death, case reports of idiopathic rhabdomyolysis with COVID-19 infection[56]
Procalcitonin	Normal in viral infection alone, elevation suggests bacterial co-infection[54]
Ferritin	Elevated in severe disease[27] biomarker seen in immunopathogenesis ("cytokine storm"), especially in secondary hemophagocytic lymphohistiocytosis[24]
IL-6	Elevation associated with disease severity
BNP/troponin*	Elevated in severe disease without evidence of primary coronary ischemia or heart failure etiology;[57] do not check routinely unless clinical suspicion for either
Influenza/RSV/respiratory viral panel	From ~6% to 22% (40% in pediatrics) co-infection rate[53,54,58]

*BNP/troponin are frequently elevated in these patients, with unclear mechanism. Per the American College of Cardiology, clinicians are advised to measure only troponin and BNP if suspecting diagnoses of acute myocardial infarction from coronary disease or heart failure, respectively. These elevations alone do not signify these disease processes in the context of COVID-19, as the virus is believed to play a direct role in the elevation of these markers. Viral myocarditis has been postulated as a potential etiology, but further research needs to be done to investigate this.

Source from American College of Cardiology

Data from the CDC released on March 17, 2020 shows a disconcerting trend in hospitalization rates in the younger-age demographic. **Table 6** shows the latest rates, with an alarming rate of hospitalization of up to 20% in individuals aged 20 to 44 years. The good news for the pediatric population is that there have been no deaths reported in the United States at the time of publication. (See the "Pediatric Population" section.)

Table 6. Hospitalization, Intensive Care Unit Admission, and Case-Fatality Percentages for Reported COVID-19 Cases, by Age Group; United States, February 12–March 16, 2020

Age Group (yr) (Number of Cases)	%*		
	Hospitalization	ICU Admission	Case-Fatality
0–19 (123)	1.6–2.5	0	0
20–44 (705)	14.3–20.8	2.0–4.2	0.1–0.2
45–54 (429)	21.2–28.3	5.4–10.4	0.5–0.8
55–64 (429)	20.5–30.1	4.7–11.2	1.4–2.6
65–74 (409)	28.6–43.5	8.1–18.8	2.7–4.9
75–84 (210)	30.5–58.7	10.5–31.0	4.3–10.5
≥ 85 (144)	31.3–70.3	6.3–29.0	10.4–27.3
Total (2449)	**20.7–31.4**	**4.9–11.5**	**1.8–3.4**

*Lower bound of range = number of persons hospitalized, admitted to ICU, or who died among total in age group; upper bound of range = number of persons hospitalized, admitted to ICU, or who died among total in age group with known hospitalization status, ICU admission status, or death.

Abbreviation: ICU, intensive care unit.

Source from Centers for Disease Control and Prevention

Imaging

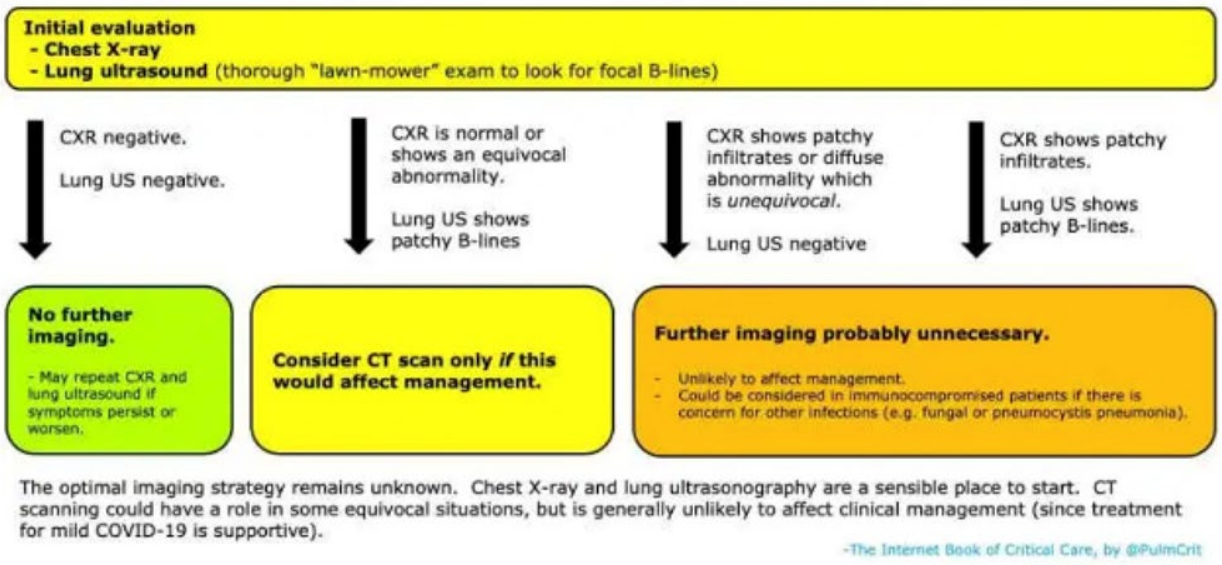
Findings on chest imaging in COVID-19 have been similar to findings seen in previous years from the SARS-CoV-1 and MERS-CoV outbreaks. A cohort analysis of 41 COVID-19 patients found all but 1 with bilateral lung involvement.[21,59] A study of computed tomography (CT) scans of 21 COVID-19 patients showed 3 (21%) with normal CT scans; 12 (57%) with ground-glass opacity only; 6 (29%) with ground-glass opacity and consolidation at presentation; and interestingly, 3 (14%) with normal scans at diagnosis. Fifteen patients (71%) had 2 or more lobes involved, and 16 (76%) had bilateral disease.[60] Of the 18 patients with positive findings on chest CT, all had the presence of ground-glass opacities, with 12 of the 18 having concomitant lobar consolidations.[60]

Data on 101 cases of COVID-19 pneumonia analyzed retrospectively from 4 institutions in Hunan, China found lesions present on CT were more likely to show a peripheral distribution (87.1%), bilateral involvement (82.2%), lower lung predominant (54.5%), and multifocal (54.5%).[61] These findings, specifically the peripheral distribution of lesions, reflect positively on the ability of lung ultrasound to detect COVID-19 pneumonia.

Given the rate of nosocomial spread of the virus, the resource-intensive nature of obtaining CT scans in these patients, and the risk of transporting unstable hypoxemic

patients, routine CT scans are not recommended in COVID-19 patients, as it rarely leads to a change in management. The American College of Radiology supports the use of CT sparingly, mainly in hospitalized symptomatic patients who may have other pathologies that need to be considered.[62] **Figure 6** presents a schema for imaging in patients with suspected COVID-19 pneumonia.

Figure 6. Possible Schema for Imaging in Patients With Respiratory Symptoms and Suspected COVID-19 Pneumonia[42]



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Recent literature as well as anecdotal reports from Italy offer support for using lung ultrasound as a way to screen patients with suspected COVID-19 pneumonia. For evaluation of pneumonia and/or adult respiratory distress syndrome (ARDS), lung ultrasound gives results that are similar to chest CT and are superior to standard chest radiography, with the added advantage of ease of use at point of care, repeatability, absence of radiation exposure, and low cost.[63] **Table 7** details findings on lung ultrasound as they correlate to findings on chest CT, with COVID-19 commonly resulting in lung pathology in the posterior lobes.[64] In Italy, this has proven to be a useful screening tool. **(See Table 1.)**

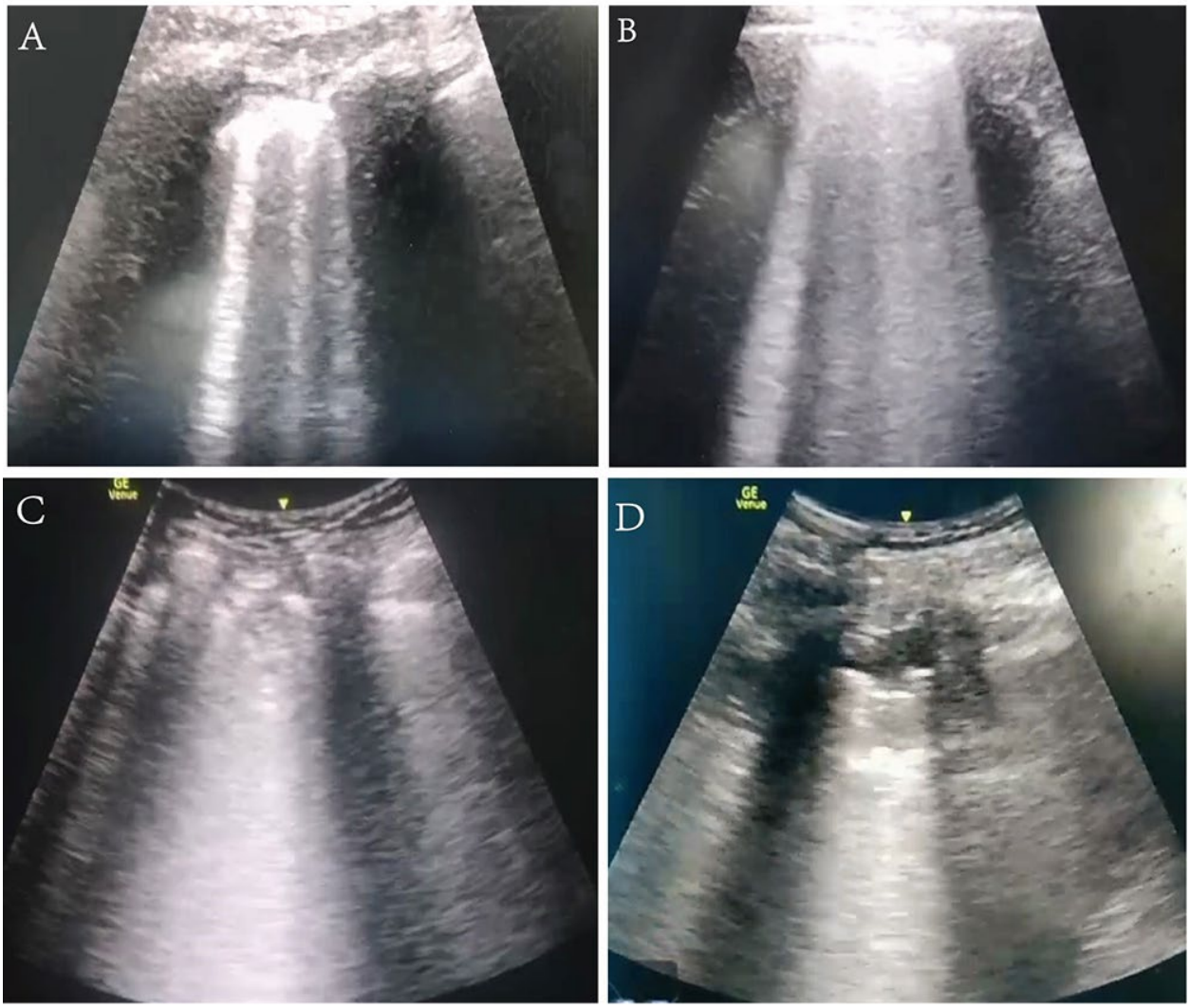
Table 7. CT and Ultrasonographic Features of COVID-19 Pneumonia[64]

Lung Computed Tomography	Lung Ultrasound
Thickened pleura	Thickened pleural line
Ground-glass shadow and effusion Pulmonary infiltrating shadow	B lines (multifocal, discrete, or confluent) Confluent B lines
Subpleural consolidation	Small (centromeric) consolidations
Translobar consolidation Pleural effusion is rare	Both nontranslobar and translobar consolidation Pleural effusion is rare
More than 2 lobes affected	Multilobar distribution of abnormalities
Negative or atypical lung CT images in the super-early stage, then diffuse scattered or ground-glass shadow with the progression of the disease, further lung consolidation	Focal B lines is the main feature in the early stage and in mild infection; alveolar interstitial syndrome is the main feature in the progressive stage and in critically ill patients. A lines can be found in the convalescence; pleural line thickening with uneven B lines can be seen in patients with pulmonary fibrosis

Reprinted by permission from Springer Nature: Springer Nature, *Intensive Care Medicine*. Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. Qian-Yi Peng, Xiao-Ting Wang, Li-Na Zhang, and Chinese Critical Care Ultrasound Study Group (CCUSG). Copyright Springer Nature, 2020.

With increasing disease severity, an evolution of findings on lung ultrasound may be seen.[64] **(See Figure 7.)**

Figure 7. Evolution of Findings on Lung Ultrasound from Least Severe to Most Severe in a Patient with COVID-19 Pneumonia



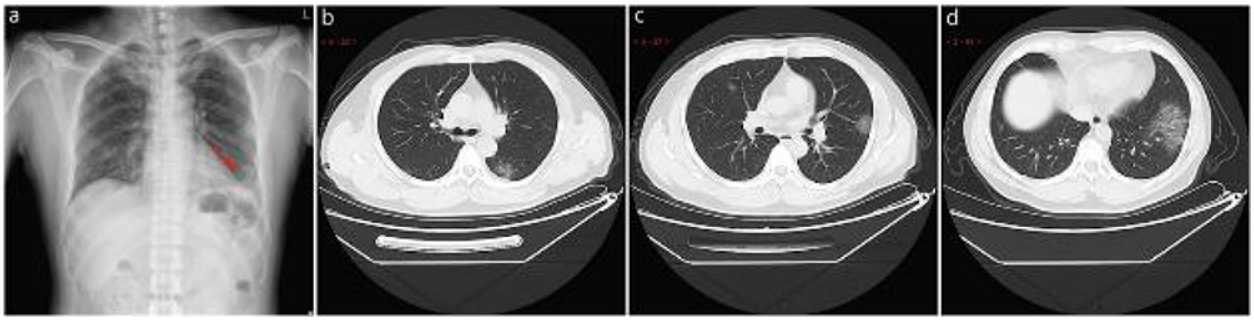
View A: Least severe. Mild ground-glass opacity on CT scan correlates to **scattered B-lines.**
View B: More confluent ground-glass opacity on CT scan correlates to **coalescent B-lines ("waterfall sign").**
View C: With more severe disease, **small peripheral consolidations** are seen on CT scan and ultrasound.
View D: In the most severe form, the **volume of consolidated** lung increases.

Here is a YouTube video of an ultrasound scan of a patient with COVID-19 pneumonia [Courtesy Giovanni Volpicelli, MD]: https://youtu.be/0REiKhbZm7s

Healthcare providers interested in receiving training to spot characteristic changes in the lung parenchyma in patients with COVID-19 can reference a recently published article by Huang et al, which has multiple examples of ultrasound images correlated to findings on high-resolution chest CT.[65] This article and the images can be seen in Research Square

The article, "A Rapid Advice Guideline for the Diagnosis and Treatment of 2019 Novel Coronavirus (2019-nCoV)-Infected Pneumonia (standard version)," published in the journal, *Military Medical Research,* provides rapid advice guidelines and diagnostic imaging of several cases.[39] **Figure 8** presents a typical x-ray and CT images of a patient with COVID-19.

Figure 8. X-Ray and Computed Tomography Imaging of COVID-19 Pneumonia



Typical CT /X-ray imaging manifestation (case 2). A 51-year-old male with general muscle ache and fatigue for 1 week, fever for 1 day (39.1°C), anemia. Laboratory tests: normal white blood cells (9.24 × 109/L), lymphocytes percentage (5.1%), decreased lymphocytes (0.47 × 109/ L), decreased eosinophil count (0 × 109/L), increased C-reaction protein (170.91 mg/L), increased procalcitonin (0.45 ng/mL), increased erythrocyte sedimentation rate (48 mm/hr). Imaging examination: **(a)** shows patchy shadows in the outer region of the left lower lobe; **(b)** shows large ground-glass opacity in the left lower lobe; **(c)** shows subpleural patchy ground-glass opacity in posterior part of right upper lobe and lower tongue of left upper lobe; and **(d)** shows large ground-glass opacity in the basal segment of the left lower lobe.

Available at Military Medical Research

The article, "Evolution of CT Manifestations in a Patient Recovered from 2019 Novel Coronavirus (2019-nCoV) Pneumonia in Wuhan, China," published in the journal *Radiology*, published 6 images of the evolution of chest imaging of a 42-year-old male patient infected with COVID-19 who recovered over 31 days.[66]

Management

In the case of infection with any of the coronavirus strains, there is no approved treatment specific to the virus. Many patients with confirmed COVID-19 pneumonia in a recent *JAMA* study received broad-spectrum antibacterial therapy (moxifloxacin, 89 [64.4%]; ceftriaxone, 34 [24.6%]; azithromycin, 25 [18.1%]) with most receiving anti-influenza therapy (oseltamivir, 124 [89.9%]), and some additionally receiving steroids (glucocorticoid therapy, 62 [44.9%]).[2] Given the evolving nature of this pandemic, clinicians may be well served by seeking the guidance of nations or health systems that have implemented proven treatment and management protocols. One such guidance from Belgium, entitled "Interim Clinical Guidance For Patients Suspected Of/Confirmed With Covid-19 In Belgium". Recommendations from the Italian Society of Infectious and Tropical Diseases can be found here (published in Italian)

For an additional example, see **Figure 9** for the Boston Medical Center's COVID-19 treatment protocol.

Figure 9. Boston Medical Center COVID-19 Resources

- **COVID-19 Adult Treatment Protocol**
- **COVID-19 Pediatric Treatment Protocol**
- **COVID 19 Consolidating Care to Decrease Caregiver Touch**
- **Nasopharyngeal Specimen Collection Instructions**
- **COVID-19 Airway Management**
- **COVID-19**

For these Clinical Procedures and additional resources from Boston Medical Center, visit:

www.bmc.org/covid-19-information-employees/screening-and-testing

Source: Boston Medical Center

Antivirals

Considering the lack of direct evidence with regard to treatment of COVID-19, recently proposed guidelines have been built largely on treatment guidelines for SARS-CoV, MERS-CoV, and influenza infections. Currently, there are weak recommendations for alpha-interferon atomization inhalation twice/day, and lopinavir/ritonavir orally twice/day; however, evidence supporting these in reducing the incidence and mortality of ARDS in patients infected with SARS-CoV-1 and MERS-CoV are limited to case series and case reports.[39] A recent systematic review showed that lopinavir/ritonavir's anticoronavirus effect was seen mainly in its early application, and no significant effect was seen in late application of therapy.[67] A recently published randomized controlled trial in *The New England Journal of Medicine* on 199 hospitalized COVID-19 patients found no benefit to

mortality or time to clinical improvement with lopinavir-ritonavir treatment. Positive trends in nonprimary outcomes, such as complications of acute kidney injury, serious infections, and rate of noninvasive or invasive mechanical ventilation were noted; however, the study ended enrollment as another study using remdesivir became available.[68] At this time, the use of combination antivirals in the treatment of COVID-19 is controversial, as there are currently no randomized controlled trials in humans to support their use.[69,70]

Remdesivir has recently been recognized as a promising antiviral drug against a wide array of RNA viruses, including SARS-CoV-1 and MERS-CoV infection in vitro and in nonhuman primate models.[71] Recent in vitro studies conducted on COVID-19 have found that remdesivir and chloroquine inhibit viral infection of cells with low micromolar concentration with a high selectivity index.[72] There are ongoing clinical trials in multiple countries testing the efficacy of remdesivir, though at this time this drug is available only for compassionate use in severe COVID-19 cases, and is not available commercially.

A recent open-label non-randomized control study between treatment with favipiravir and interferon-alpha (treatment group) and lopinavir/ritonavir and interferon-alpha (control group) found significant reduction in the time to viral clearance (median 4 versus 11 days, $P < .001$) and improvement rate on chest CT scan at day 14 (91.4% to 62.2%, $P = 0.004$); it should be noted, severely ill patients were excluded from this study.[73]

Glucocorticoids

In a systematic review in the Chinese literature of treatments for SARS-CoV-1, 14 studies were identified in which steroids were used. Twelve studies were inconclusive and 2 showed potential harm. One study reported diabetes onset associated with methylprednisolone treatment.[74] Another uncontrolled, retrospective study of 40 SARS patients reported avascular necrosis and osteoporosis among corticosteroid-treated SARS patients.[59] A randomized, double-blind, placebo-controlled trial measured SARS-CoV-1 plasma viral load across time after fever onset and found corticosteroid use within the first week of illness was associated with delayed viral clearance.[75]

However, a recent study performed in China examining risk factors associated with the development of ARDS in COVID-19 patients found that treatment with methylprednisolone decreased the risk of death among patients with ARDS (hazard ratio, 0.38; 95% CI, 0.20-0.72).[45] These data lend support to the theory that deterioration in COVID-19 patients occurs secondary to an immunopathogenesis and development of a “cytokine storm,” which can be mitigated by administration of glucocorticoids in patients with severe ARDS.

Other Therapeutic Agents

Cytokine storm is being increasingly examined as a culprit behind the rapid deterioration of COVID-19 patients several days to weeks after initial infection by SARS-CoV-2, which raises the possibility of utilizing inflammatory cell receptor blockers and stem cell therapy as potential therapeutic agents. Multicenter clinical trials are underway investigating tocilizumab (IL-6 receptor blocker) in the treatment of COVID-19 pneumonia.[20] A more comprehensive list of ongoing investigations and trials into novel therapies against SARS-CoV-2 can be found in Monthly Prescribing Reference.

A considerable amount of literature has attributed a variety of antiviral and immunomodulatory effects to chloroquine, including the suppression of IL-6, a cytokine believed to play a significant role in the deterioration of COVID-19 patients into severe ARDS.[20,76] Chloroquine has also been shown to act as an effective antiviral medication in animal models infected with avian influenza and SARS-CoV-1.[77,78] Unpublished data emerging from China suggest that chloroquine has been studied as a treatment for COVID-19, with favorable results.[79] The Guangdong Provincial Department of Science and Technology and the Guangdong Provincial Health Commission recently submitted an expert consensus report that recommended chloroquine treatment of new coronavirus pneumonia with a treatment regimen of 500 mg orally twice daily for patients without contraindications.[80] A recent study published in *Clinical Infectious Diseases,* using physiologically based pharmacokinetic models, found increased potency of hydroxychloroquine over chloroquine (EC50 = 0.72 µM vs 5.47 µM, respectively) in lung tissue. This study recommends a 400 mg loading dose twice daily for 1 day, followed by a 200 mg maintenance dose twice daily for 4 days.[81] Clinical trials are underway to formally investigate the use of these medications both as a therapeutic and prophylactic agent against COVID-19 in humans.[82] A recent nonrandomized clinical trial of 20 patients found hydroxychloroquine treatment to be significantly associated with viral load reduction and disappearance in COVID-19 patients, with this effect increased by the addition of azithromycin. Hydroxychloroquine dosing was 600 mg daily, and azithromycin was 500 mg on the first day followed by 250 mg daily for 4 days.[83] (Note that the publisher states, “This article is a preprint and has not been peer reviewed. It reports medical research that has yet to be evaluated and so should not be used to guide clinical practice.”) Clinical trials are underway to formally investigate the use of these medications both as a therapeutic and prophylactic agent against COVID-19 in humans

Fluid Management

There is no significant literature at present on optimal fluid management in patients with COVID-19, nor is there literature that describes new-onset congestive heart failure secondary to the virus. As previously described, a leading theory in the pathophysiology of rapidly deteriorating COVID-19 patients is that ARDS (noncardiogenic pulmonary edema) is brought on by a hyperinflammatory state. Given that this is not a form of distributive or hypovolemic shock that is seen in bacterial sepsis and the resulting pulmonary edema is the primary life-threat to those with severe COVID-19, the authors recommend a judicious approach to fluid resuscitation on a case-by-case basis.

Airway Management

In patients who deteriorate and require ICU-level care, clinicians should consider noninvasive ventilation (NIV), mechanical ventilation, or extracorporeal life support, if necessary.[39] The development of ARDS and respiratory decompensation plays a central role in the pathogenesis of COVID-19. In this sense, the following treatment principles are key in managing COVID-19 patients:

- Hemodynamic management, with vasopressor support if necessary
- Nutritional support
- Blood glucose control
- Expeditious evaluation and treatment of nosocomial or concomitant bacterial pneumonia
- Prophylaxis against deep vein thrombosis and gastrointestinal bleeding
- Proper patient positioning to aid oxygenation and ventilation

Preliminary unpublished data from Andrea Duca, MD in an ED in Bergamo, Italy shows that from February 29 to March 10, 2020, the rate of patients presenting to the ED with suspected COVID-19 who needed admission for oxygen therapy increased by 138%. Among those admitted patients, 31% were still hypoxic on maximal oxygen therapy and started on ventilatory support in the ED (81% CPAP, 7% NIV, 12% invasive ventilation), with 82% showing criteria for moderate to severe ARDS.

Noninvasive Ventilation

Data from China and Italy suggest that COVID-19 patients who are hypoxemic respond well to PEEP, indicating a crucial role for NIV as a therapeutic and stopgap measure to prevent intubation.[45] The statistics from retrospective analyses in China indicate that up to 30% of admitted patients required NIV,[84] while early reports from Italy indicate figures approaching 31%. Given current epidemiological trends, these requirements are likely to outpace the current capacity of most, if not all, hospitals if aggressive preparatory measures are not taken. Based on the current data from China and Italy, we recommend the following:

1. Aggressively expand your hospital's storage of NIV devices and ventilators. In an effort to combat nosocomial spread and aerosolization of the SARS-CoV-2 virus, prioritize the following:
    a. Dual-limb NIV devices with expiratory filters, such as the PB840 ventilator
    b. Viral filter proximal to leak port on single-limb devices
    c. Single-limb NIV devices helmet CPAP with viral filters before PEEP valves
2. Dedicate a portion of the ED and inpatient units for COVID-19 patients, with patient bays and rooms equipped to administer NIV.

See Figures 10, 11, and 12 for image of single-limb NIV device, demonstration of wear, and a helmet CPAP with viral filter before PEEP valve .

Figure 10. Viral Filter Leak Port; Single-Limb NIV Device

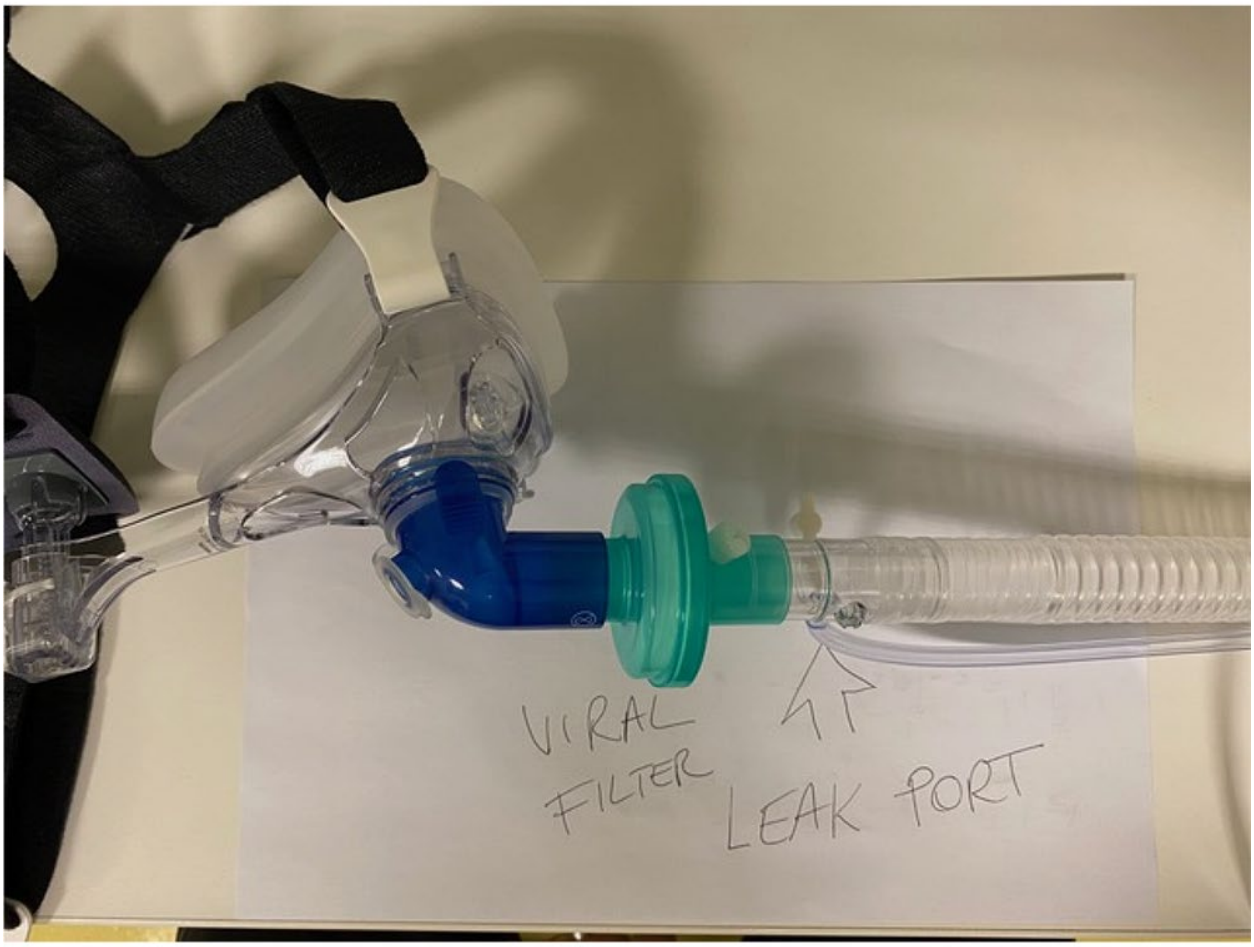


Image courtesy of Andrea Duca, MD.

Figure 11. Demonstration of Wear

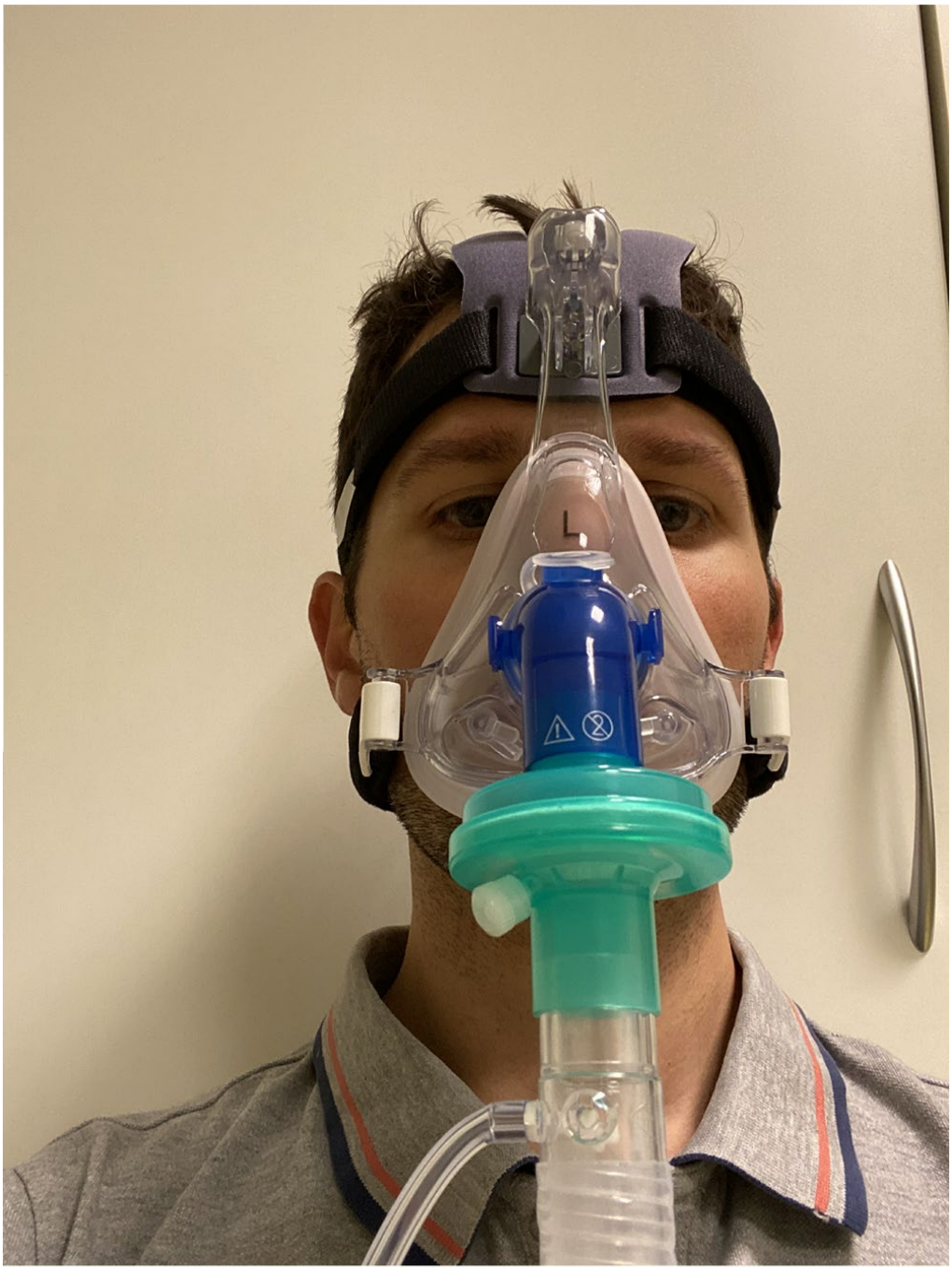


Image courtesy of Andrea Duca, MD.

Figure 12. Viral Filters Before PEEP Valve on Helmet CPAP Device

Used with permission of Andrea Duca, MD

Rapid Sequence Intubation for Invasive Ventilation

In the event a patient presents in severe respiratory distress or fails prior use of NIV, the clinician must prepare for invasive ventilation and endotracheal tube intubation. **See Table 8** for rapid sequence intubation (RSI) steps.

Table 8. Steps for Rapid Sequence Intubation[42]

- Personal Protective Equipment (PPE)
  - N95 or PAPR
  - Face shield +/- goggles
  - Gloves (consider double-gloving), gown
  - Disposable cap to cover head/hair
- Premedication
  - High-dose paralytic (rocuronium, at least 1.2 mg/kg)
- Equipment
  - Video laryngoscope (to minimize proximity to patient)
  - Bag-valve mask (BVM) with PEEP valve and viral filter
  - Viral filter on exhalation port of ventilator, to create sterile closed circuit
- Procedure
  - Performed by most experienced staff
  - Limit the number of people in the room
  - During episodes of apnea
    - If using BiPAP, continue with backup rate
    - If using BVM, hold mask (with PEEP valve attached) with jaw thrust to prevent collapse of alveoli), but avoid bagging the patient, if possible, as this may potentially aerosolize viral particles
  - Inflate endotracheal tube (ETT) cuff prior to ventilation
  - Secure ETT at precalculated depth
- Post-Procedure:
  - Doff PPE using meticulous doffing procedure described in **Table 2**.

Preoxygenation

There is ongoing controversy as to the role of preoxygenation and the possible spread of viral particles while utilizing the typical techniques. A review on this subject can be found in EMcrit. In the meantime, the commonly utilized choices are:

- BiPAP with a 2-tube system and viral filter, or
- 100% FiO_2 nonrebreather mask

Invasive Ventilation Strategies

For a brief synopsis on the indications, principles, and various types of mechanical ventilation, please see Hickey et al. For COVID-19 patients, special emphasis should be placed on the "Lung Protective Strategy" section, based on the ARDSnet trials, which showed that low tidal volume ventilation in patients with ARDS improved mortality.[85] Briefly:

Tidal volume (TV) should be initially set at 6 mL/kg based upon ideal body weight. As patients develop acute lung injury and progress into ARDS, their lungs become progressively recruited and develop shunts, which leads to decreased functional lung volume. A low tidal volume strategy offsets the decreased functional lung volume. Tidal volume should not be adjusted based on minute ventilation goals. Respiratory rate is adjusted based upon minute ventilation goals and the acid-base status of the patient. An initial rate of 16 breaths/min is appropriate for most patients to achieve normocapnia.[86]

Disaster Ventilation

In disaster situations when the number of patients requiring mechanical ventilation outpaces the number of available ventilators, ventilators can be rigged to split airflow to multiple patients. Click here for a video tutorial on how to accomplish.

The key take-aways for this maneuver include the following:

- Use pressure-cycled ventilation over volume-cycled to maintain consistent flow to all patients on the other end of the ventilator, with high PEEP (COVID-19 patients are PEEP responders) and low driving pressure (to achieve lung protection).
- Vents should be set at a continuous mandatory rate. If this is not possible (as is the case with some modern ventilators), increase the threshold as high as possible so that it is impossible for any single patient to "trigger" delivery of a breath.
- You will have to be comfortable with permissive hypercapnia, as ventilation is suboptimal with this setup. For patients with substantial acidosis, IV bicarbonate can be used as a stopgap measure to support pH.
- Ideally, all patients hooked to the same ventilator should have similar severity of lung injury, and hence should tolerate similar PEEP and FiO_2 settings.
- Viral filters should be used to prevent cross-contamination of infectious pathogens between patients.
- Paralytics with sedation can be used as a final measure to prevent hyperventilating patients from triggering the ventilator.

Pediatric Population

Children seem to have been relatively spared from the worst complications and mortality of this disease, as noted in the CDC rates of hospitalization per age group. **(See Table 6.)** To date in the United States, and from our co-author's experience in Northern Italy, there have been no reported deaths in children. However, in a prepublication paper released on March 16, 2020 in the *Journal of Pediatrics*, Dong et al analyzed 2143 children in China with suspected and confirmed SARS-CoV-2 infection and found that almost "4% of children were asymptomatic, 51% had mild illness and 39% had moderate illness. About 6% had severe or critical illness, compared to 18.5% of adults. One child, a 14-year-old boy, died."[87] The study also found that infants had higher rates of serious illness when compared with older children. Approximately 11% of infants had severe or critical cases compared to 7% of children ages 1 to 5 years; 4% of those 6 to 10 years; 4% of those 11 to 15 years; and 3% of those aged 16 years and older. There are several theories speculating on the vast differences between adults and children, such as "higher levels of antibodies against viruses or different responses from their developing immune systems."[87] Another theory is related to the relative lack of or poorly developed ACE2 receptors in children, which prevents the virus from being able to bind as well to children's cells. Wu et al reported in their Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention of approximately 1000 children under the age of 19, no reported deaths in children younger than 9 years of age.[84] In a recent correspondence to the *New England Journal of Medicine*, researchers from China found that of the 171 cases confirmed to have SARS-CoV-2, there was only 1 death in a 10-month old child, who had multiple co-morbidities.[88]

In a small retrospective study in China, 20 confirmed SARS-CoV-2-positive pediatric patients were analyzed with CT scans of their chests as well as laboratory markers, including procalcitonin. The authors found that procalcitonin was elevated in 16/20 patients, chest CTs showed consolidation with surrounding halo signs in 10/20 patients, and 12/20 showed ground-glass opacities. It was also suggested that underlying co-infection may be more common in children (8/20), and a consolidation with surrounding halo sign is considered a typical sign for this population.[58] Even though the pediatric population may be spared the morbidity and mortality seen in adults, clinicians should be aware that they may infect more vulnerable populations and should encourage social distancing. Further research in the American pediatric population will better help the understanding and management of severe disease presentations in children in the United States.

Pregnant Patients

The data on pregnant patients with COVID-19 still remains sparse.[89] Generally, pregnant women with SARS-CoV-2 infection share the same characteristics of nonpregnant women with the virus. In a retrospective review of 9 patients, Chen et al analyzed the risk of maternal-fetal transmission of SARS-CoV-2 and found that

intrauterine transmission from SARS-CoV-2-positive mothers was shown to be unlikely.[90] Additionally, in those patients, they found very few complications related to pregnancy, unlike the complications that were characteristic of pregnant women with SARS.[91,92] . Clearly, larger studies will need to be conducted to better evaluate the risk of vertical transmission between mother and fetus with SARS-CoV-2 infection.

Shared Decision-Making and COVID-19

--Marc Probst, MD

Shared decision-making is a collaborative process in which patients and providers make healthcare decisions together, taking into account scientific evidence, the clinician's experience, as well as the patient's values and preferences. Although the scientific evidence underlying the testing and treatment of SARS-CoV-2 infection is nascent and evolving rapidly, certain knowledge is known and extrapolation from other serious infectious diseases is justified. There are at least 2 clinical scenarios related to COVID-19 that may be appropriate for SDM: (1) testing for SARS-CoV-2 in mildly symptomatic patients and (2) goals-of-care discussion in critically ill patients.

Given that there are no treatments proven to be beneficial for COVID-19 at the time of this writing, making the diagnosis of this disease in mildly symptomatic patients may not change clinical management. Standard supportive care, as is used for typical viral upper respiratory infections, can be recommended for patients, without testing for SARS-CoV-2. These would include over-the-counter antipyretics, antitussives, decongestants, analgesics, oral fluids, and rest. Patients would also be instructed to practice self-isolation to prevent spread of COVID19 to other individuals. The current tests for SARS-CoV-2, using RT-PCR, has a sensitivity between 60% and 90% and can generate false-positive or false-negative results. Given the real possibility of a limitation in testing resources, it may be reasonable for patients with possible COVID-19 to forgo testing, assume that they have the virus, and take the socially responsible precautions. Given the rapidly changing guidance around testing from institutions and government health agencies, adherence to your hospital, state, or local policies should be followed and explained to the patient.

Another clinical scenario that would be appropriate for shared decision-making would be endotracheal intubation for a patient in respiratory failure with a poor prognosis, either due to advanced age or severe comorbidities. This decision will be frequently encountered since ARDS is a common final pathway for many patients with COVID-19. Early studies have demonstrated high mortality rates for older patients, particularly those over age 80. In this scenario, providers could potentially engage in shared decision-making with patients or their surrogates to collaboratively decide whether or not intubation is justified. This is similar to other goals-of-care discussion around code status for patients with advanced age and/or end-stage diseases.

Looking to the Future

In our first iteration, we speculated on the future of what was not yet a pandemic. Unfortunately, the future is here, and we are in the midst of a growing pandemic that has shut down cities, nations, and continents. We may be best served to look at past events to learn from others' missteps and seek opportunities to improve for the regions of the world not yet inundated with COVID-19.

"Community spread," "stealth transmission," "social distancing," and "flattening the curve" have become common parlance as the public and medical societies attempt to understand and control COVID-19. With an R_0 value mimicking pandemic influenza, the spread and containment of SARS-CoV-2 faces unprecedented challenges.[93] We continue to find that constantly changing daily information (and misinformation) have added to the challenges to the general public as well as the medical community. *The Lancet* published an online editorial, which appeals to the medical community and the public alike to seek verified information through the CDC or WHO and avoid social media and other unverified sources for information. Many worried well patients will show up in the ED, taxing already overburdened systems. This is an opportunity for hospital leadership to develop and/or expand their telehealth options, to minimize the numbers of worried well or low-risk patients with mild symptoms overwhelming local EDs.

There are now several biotech and pharmaceutical companies racing for a vaccine for SARS-CoV-2, and although studies are promising, widespread availability and use are at least 18 months away (summer of 2021). A DNA vaccine candidate for SARS-CoV-2 has entered into human clinical trials, while 2 vector-based candidates have begun human trials; protein-based vaccines are still at the preclinical stage.[72] There are still challenges to the successful development of a vaccine due to incomplete understanding of viral transmission, pathogenesis, and immune response; and lack of optimal animal challenge models and standardized immunological assays.

Hospital Management

We believe China, Washington state, Italy, and now the New York metropolitan area should serve as examples for the rest of the world not yet inundated with SARS-CoV-2. Being prepared for an onslaught of cases is the first step all healthcare systems need to accept. Testing and isolating infected or suspected persons early has shown benefit in China, South Korea, and elsewhere, and locales such as New York City can attest to the negative effect of being unprepared for mass testing and expeditious containment of spread on its populations.

In the event of a mass influx of patients with exposure to SARS-CoV-2 or symptoms concerning for COVID-19, immediate isolation is required. If 1 infected person presents to a busy ED triage area, there is a high likelihood of spreading the virus and potentially contaminating others. The CDC recommends placing ample touchless hand sanitizer stations and easy-to-dispense boxes of face masks at entrances to the ED and hospital.

They also recommend placing signs that advise anyone entering the facility to "immediately put on a mask and keep it on during their assessment; cover their mouth/nose when coughing or sneezing; use and dispose of tissues carefully; and perform hand hygiene after contact with respiratory secretions."[94] The authors recommend hospital and departmental leadership pursue the following directives:

1. Expand availability of negative pressure rooms where possible, with priority given to COVID-19 patients to occupy these spaces.
2. In larger hospital systems, consider designating a single hospital as the treatment center for COVID-19 patients, to streamline use of resources and prevent nosocomial spread of SARS-CoV-2.
3. Maintain flexibility in the layout of the ED and triage processes for changing dynamics, as the SARS-CoV-2 virus spreads through the community and overwhelms the traditional ED flow patterns.
4. Emergency management should have a disaster plan in place that addresses pandemics, over-capacity patient volumes, and potential staffing shortages.
5. Coordinate resource management and allocation with local, state, and federal government agencies such as the Federal Emergency Management Agency (FEMA) and the Department of Defense (DoD).
6. Immediately develop policies for resource management and rationing of medical supplies in conjunction with the ethics committee, risk management, and palliative care services.
7. Health systems should develop and implement antibody testing for SARS-CoV-2 in order to preserve the health of our frontline healthcare workers, and limit exposure to the non-immune.
8. Train and hire additional environmental services workers who can expedite the turnover of beds in the ED and around the hospital. An unclean isolation room during a pandemic risks a potential COVID-19 patient infecting the ED and elsewhere.

The single best way to save the most people and reduce morbidity is to be proactive and not reactive. Those of us in the midst of this crisis wish we could have done things differently and implemented the above recommendations from the moment we encountered patient zero. Our lack of early testing and strict isolation run counter to what epidemiologists recommend to control infectious outbreaks. Please learn from our mistakes.

Table 9. Helpful Resources for COVID-19

Organization	Link
United States Centers for Disease Control and Prevention	Coronavirus Disease 2019 (COVID-19)
World Health Organization	Coronavirus disease (COVID-19) outbreak
Johns Hopkins University	COVID-19 Global Case Tracker
United States Department of Labor, Occupational Safety and Health Administration	COVID-19 Additional Resources
American College of Emergency Physicians	COVID-19 Clinical Alert
The Lancet	COVID-19 Resource Centre

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Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study will be included in bold type following the references, where available.

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