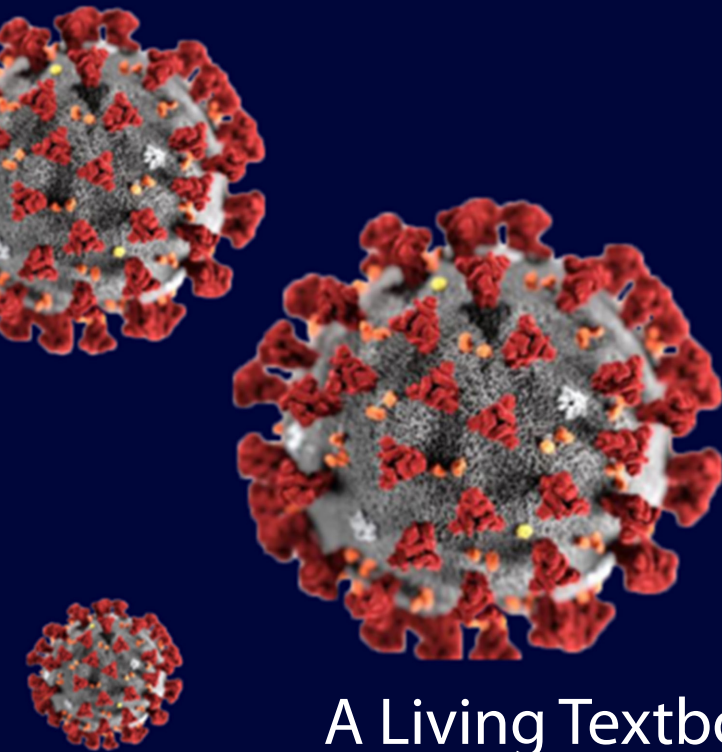


Carey Kriz • Naiyer Imam  
Sarah Zaidi  
*Editors*

# BREAKING DOWN COVID-19



**A Living Textbook**

Publication of First Medicine and Global Clinical Partners

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# Introduction to COVID-19 Living Textbook

## List of Abbreviations

COVID-19	Coronavirus disease 2019
HIV	Human immunodeficiency virus
MERS	Middle East respiratory syndrome
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

The world is amidst a pandemic that is presenting one of the greatest public health challenges of the twenty-first century. A new coronavirus has jumped the interspecies barrier, and it possesses the capability of efficient person-to-person transmission and selectively kills older people and those with underlying chronic conditions. Since its emergence the new coronavirus has resulted in 43.7 million infections and over 1 million deaths as of October 25, 2020—20% of deaths are in the United States followed by Brazil (14%), India (10%), Mexico (7.8%), and the United Kingdom (4%).<sup>1</sup>

The new disease emerged in December 2019 in Wuhan, China, and the early cases appeared to be associated with a local wholesale fish and live animal market.<sup>2</sup> The cluster of patients exhibited respiratory features of pneumonia and acute respiratory distress syndrome as seen in the severe acute respiratory syndrome (SARS) coronavirus of 2002–2003, leading the scientists to suspect a virus of zoonotic origins. On December 31, the Chinese authorities informed the World Health Organization (WHO) of the outbreak, putting the organization on emergency footing.<sup>3</sup> The WHO issued comprehensive technical guidance online with advise to all countries on how to detect, test, and manage emerging infections based on previous experience with SARS and the Middle East respiratory syndrome (MERS) outbreak of 2012.<sup>4</sup> In mid-January, Chinese authorities announced a novel coronavirus with genetic structure similar to SARS (80%), and with its origins in bats, it was the cause of the new disease.<sup>5</sup> The virus was officially named the *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) and the disease it caused the *Coronavirus Disease 2019*, or COVID-19.<sup>6</sup>



Chinese authorities tried to contain the outbreak by imposing quarantines, social distancing, and testing, contact tracing, and isolating infected people. The entire Wuhan city of 11 million and Hubei Province of nearly 60 million, and later a quarter million people in other parts of China, were put under lockdown.<sup>7</sup> But global transportation systems having morphed over a period of 100 years from slow trickles of population from one place to another to instantaneous shifts between continents made it difficult to contain outbreaks of COVID-19. Forty years earlier, the spread of HIV in the world had established how quickly a virus could spread between continents through simple air travel by an infected person. In this century, SARS, MERS, Zika, and the Ebola virus outbreaks all demonstrated the ease with which travelers could spread emerging pathogens. SAR-CoV-2 is no different, and it is even more efficient at transmission.<sup>8</sup>

In the first 3–4 months of the outbreak, person-to-person transmission taking place before the infected person showed any symptoms of the disease, undetected cases of COVID-19 infection accounted for 79% of documented infections.<sup>9</sup> In less than two months, SARS-CoV-2 went from a public health emergency to a disease of pandemic status, declared such on March 11, 2020, by WHO.<sup>10</sup> At that time, there were 118,000 cases and 4291 deaths. Over 90% of cases were in just four countries: China (80,955 cases and 3162 deaths), Italy (10,149 cases and 631 deaths), Iran (8042 cases and 291 deaths), and South Korea (7755 cases and 60 deaths).<sup>11</sup> But the number of cases in countries kept increasing rapidly.

As SARS-CoV-2 spread rapidly encountering a population that had no immunity and health-care systems that were unprepared, the virus claimed many lives. Although less deadlier than SARS, which had a case fatality rate of 10%, and the influenza pandemic of 1917 that had a mortality risk of 2%, COVID-19 appeared to be more deadly than seasonal influenza (0.1% mortality risk).<sup>12</sup> Scientists estimated that the mortality risk for COVID-19 ranged from 0.2% to 1.0%, and was to increase substantially for people aged 60 years and older (6.38%) compared with those under 60 years (0.318%). The highest case fatality rates were seen in people in their 70s (8.61%) and 80s (13.4%) years of age.<sup>13</sup> However, a number of other factors such as sex (males), chronic comorbidities such as diabetes, obesity, cardiovascular disease, hypertension, and other social determinants were emerging as risk factors for COVID-19 infection and mortality.<sup>14, 15</sup>

As a new disease, COVID-19 required an effective response to slow down spread and prevent health systems from becoming overwhelmed. Countries implemented travel restrictions and full or partial lockdowns,<sup>16</sup> which slowed down transmission but had devastating socioeconomic consequences and resulted in a global recession.<sup>17</sup> Nonetheless, it was evident that basic public health measures such as testing, tracing, isolating infected cases and quarantining others, wearing facemasks, and practicing good hand hygiene were important interventions for reducing transmission and mortality.<sup>18</sup> Over the past 10 months, promising new vaccines and a number of existing antiviral drugs and other treatments have emerged and are being used to manage the disease.<sup>19–21</sup>

Since its interspecies jump, the global public health and medical communities have learned a lot about the virus. An unprecedented amount of information has been

published on COVID-19, with tens of thousands of papers being made available for free.<sup>22</sup> The sheer deluge of publications makes it difficult to keep up with the scientific literature and to assess the quality of publications given that many are in the form of preprints awaiting peer-review process. In the face of the flood of scholarly outputs, the impetus for putting together an online textbook is to make available, and easily accessible, information that has been carefully curated and reviewed from the public domain in one place, and to update it as new information comes forward.

The *COVID-19 Living Textbook* is prepared by 55 experts (medical doctors, social scientists, and medical students, who are experts in their field and many of them have been working on the frontline of the COVID-19 response). It is aimed at a wide range of audiences, including clinicians, public health specialists, social scientists, and the general public. Twenty-four chapters cover a range of topics that are divided into four sections.

- Section 1: Chapters 1, 2, 3, and 4 introduce SARS-CoV-2 and COVID-19, and include the timeline of events; the virology and immunopathology, transmission, prevention; and risk factors for COVID-19; and outpatient management of mild to moderate infection.
- Section 2: Chapters 5–18, forming the bulk of the text, focus on the system responses by the body to COVID-19 and clinical management in hospitals, including in children and adolescents (Chapter 15). Chapter 17 discusses the management of severe cases of COVID-19, and Chapter 18, given the limited available data, examines postrecovery complications and long-term impacts, and compares it with the experience from SARS and MERS.
- Section 3: Chapters 19, 20, and 21 review the situation with personal protective equipment, diagnostics, and treatments and vaccines.
- Section 4: The final three chapters (Chapters 22–24) discuss the systemic discrimination and inequalities that put certain groups at greater risk for the disease, public policy making and leadership, and planning for future epidemics and pandemics as new viruses that make the interspecies jump to humans and begin another evolutionary path in a new host family.

The COVID-19 pandemic, and the global response to it, has demonstrated that emerging and reemerging zoonotic diseases represent a public health challenge. It further reminds the global community about the impact of inequality, the gap between the “haves” and “have-not,” and the importance of social determinants of health. Even in the largest economies of the world, including the United States of America, those groups with less opportunity including Blacks, Hispanics, and Native American have higher rates of mortality.<sup>23</sup>

The legacy of COVID-19 will have long-lasting effects on society, including on the delivery of medicine. COVID-19 has ushered in, and with great success, telemedicine (TM) services.<sup>24</sup> TM is being used to triage and treat basic illnesses, monitor chronic diseases, and diagnose mild cases of COVID-19. While the pandemic is an unfortunate occurrence, it provides an opportunity to set up an infrastructure to deliver health care to everyone in an equitable, convenient, and cost-effective manner.

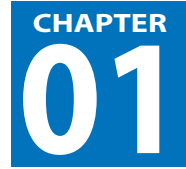
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# Overview of COVID-19



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## List of Abbreviations

CFR	Case fatality rate
MERS-CoV	Middle East respiratory syndrome coronavirus
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
COVID-19	Coronavirus disease 2019
WHO	World Health Organization

## 1.1 Introduction

The emergence of severe acute respiratory syndrome coronavirus (SARS-CoV), at the beginning of the 21st century, signaled a warning of cross-species transmissions that had the potential to rapidly spread across the globe. After SARS, several other respiratory viruses—influenza A strains of avian flu H5N1, H1N1, and H7N9 and the Middle East respiratory syndrome coronavirus (MERS-CoV)—spilled over from animal populations into humans. Earlier, the zoonotic transmission of viruses, particularly coronaviruses that existed within bat populations, was identified as a significant public health threat given the habitat loss, climate change, globalization, and the uneven public health structure.<sup>1</sup> Therefore, it should not have been a big surprise when a third human coronavirus (CoV) causing COVID-19 emerged in December 2019. Although the virus emerged in China, and spread rapidly around the world its health and economic consequences were far more complex. The emergence of COVID-19 would turn into the greatest challenge facing global leaders since World War II.<sup>2</sup>

This chapter provides a short overview of COVID-19, contextualizing it within the family of coronaviruses, cross-species transmission, and past pandemics.

## 1.2 COVID-19 Outbreak to Pandemic Status

The first cluster of patients presenting symptoms of fever, cough, myalgia and fatigue, shortness of breath, and pneumonia of unknown etiology in Wuhan city, Hubei province, central China. The majority of cases were linked to the Huanan Seafood Wholesale Market where a variety of mammals were available for sale.<sup>3</sup> The presentation of symptoms and patients association to a wet market pointed to infection of zoonotic origins similar to the SARS outbreak of 2002 and 2003. The authorities informed the local offices of the World Health Organization (WHO) on New Year's Eve, and moved to close the market the following day. Retrospective analysis of cases of pneumonia of unknown etiology, as initially classified, identified a 55-year-old person with similar symptoms who had no links to the market with disease onset in mid-November.<sup>4</sup> In the early cases, human-to-human transmission was speculated but not confirmed until two family clusters including one in which the husband transmitted the disease to his disabled wife were identified in mid-January.

Given the respiratory symptoms, Chinese doctors quickly ruled out other common respiratory pathogens, as well as SARS and the Middle East respiratory syndrome (MERS) coronaviruses, responsible for the outbreak. Samples of bronchoalveolar-lavage fluid from seven patients with severe pneumonia (six were working at the market) were sent to the Wuhan Institute of Virology for diagnosis of the causative pathogen. On January 7, 2020, it was confirmed that a novel coronavirus with 80% nucleotide sequence similarity to the SARS coronavirus and 96% similarity with bat coronavirus.<sup>5</sup> Five days later, the full genome was globally shared, a step that helped to facilitate the rapid development of diagnostic tests for the 2019 novel coronavirus (2019 n-CoV) and launched a search for multiple vaccines.

The 2019 novel coronavirus (2019 n-CoV) was renamed SARS-CoV-2<sup>6</sup> and the resulting illness as the Coronavirus Disease 2019, COVID-19.<sup>7</sup> As cases began to exponentially increase, it became evident that the virus was spreading quickly through human-to-human transmission probably since the middle of December, and that the  $R_0$  was approximately 2.2, meaning that on average each patient had been spreading the infection to more than two other people.<sup>8</sup>

Researchers soon discovered that infected individuals could transmit the virus without showing any symptoms either when they were presymptomatic or, in some cases, asymptomatic (never developing any symptoms of the disease).<sup>9</sup> This posed a great challenge to containing COVID-19. In the case of SARS and MERS, people were most infectious when they had symptoms.

The outbreak of COVID-19 also coincided with the Chinese Lunar New Year, one of the most important holidays of the year when people return to their family homes. Massive transmission had taken place as five million people (many of whom might have been incubating the virus) spread COVID-19 to other provinces in China and other countries. Chinese authorities tried to contain the outbreak by blocking

most travel into and out Wuhan, a city of 11 million, by establishing a cordon sanitaire on January 23, and later expanding it to other cities. But cases had already started to pop up in several Asian countries. Thailand reported its first case on January 13; Japan on January 15; and Korea on January 20 same day as the United States reported its first on the northwest coast; and Hong Kong, South Korea, Japan, and Taiwan on January 24. The United States reported its first case on January 20 on the northwest coast and on January 24, the first two European cases were confirmed in France.<sup>10</sup>

Within weeks, a small cluster of cases from Wuhan had started to develop into a “public health emergency of international concern,” with nearly 10,000 cases and 213 deaths, at that time mostly in China.<sup>11</sup> However, by the end of January, there were 106 cases in 19 countries. The WHO Emergency Committee advised all governments to put in place strong measures to test, detect, and isolate positive cases, trace contacts, ban large gatherings, and promote social distancing. Although SARS had a higher transmission rate,  $R_0$  of around 3<sup>12</sup> and no vaccine or treatment, the outbreak was successfully controlled by isolation of patients and infectious disease control measures.

But SARS-CoV-2 was proving harder to contain because of its insidious mode of transmission where presymptomatic or asymptomatic could inadvertently pass on the virus to others. The WHO advised countries to impose mitigation strategies and plan for health-care needs as the epidemic unfolded. Over the next 6 weeks, the world witnessed an exponential rise in cases from the initial cluster in Wuhan to 118,000 infections and 4000 deaths, even though largely in China but gradually spreading to 114 countries.

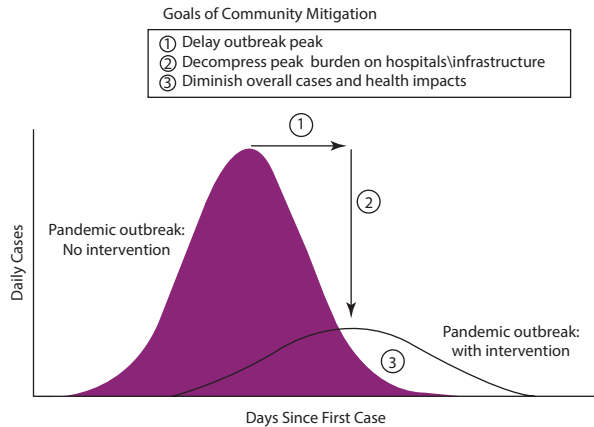
By March 11, COVID-19 cases would increase by 13-fold outside of China, forcing the WHO Director-General to officially declare a pandemic, noting that “We have rung the alarm bell loud and clear.”<sup>13</sup> With no effective treatments or vaccines and increasing numbers of infections outside China, mathematical models of COVID-19 spread started to predict millions of deaths.<sup>14,15</sup> The most high profiles of models, the Imperial Model by Neil Ferguson from Imperial College, London, predicted 2.2 million deaths in the United States and 500,000 in the United Kingdom over the year if no actions were taken to slow down the outbreak. Countries scrambled to promote hand hygiene and put into place nonpharmaceutical measures such as banning large gatherings, closing schools and businesses, and placing people under shelter-at-home orders, easing the burden on health-care systems by spreading out infected cases. The goal of “flattening the curve of COVID-19” became the defining graphic (Figure 1.1) of the pandemic as it moved West.

As countries implemented lockdowns and near-lockdowns aiming to slow down COVID-19 transmission, adverse social, psychological, and economic consequences began to emerge and disproportionately affected the poor and marginal communities (see Chapter 22). The pandemic had massive fiscal consequences, forcing governments to announce fiscal measures to protect businesses and peoples’ livelihoods.



**Figure 1.1** Flatten the curve: the goal is to reduce the incidence of cases.

Source: Center for Disease Control and Prevention, 2007.<sup>16</sup>



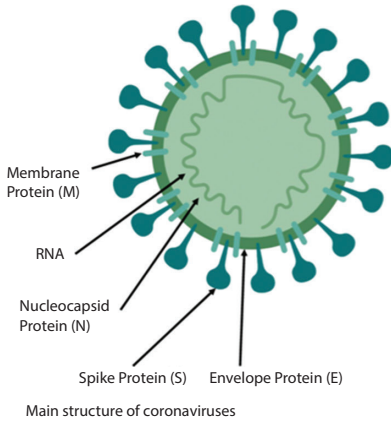
### 1.3 Human Coronaviruses

Coronaviruses, named after their spikey projections on their surface (proteins), resembling prongs of a crown, or “corona” in Latin, are enveloped, nonsegmented, single-stranded, positive-sense RNA viruses (Figure 1.2). The important structural proteins include spike (S), envelope (E), membrane (M), and nucleocapsid (N). They have a tendency for recombination and inherently high mutation rates compared with DNA viruses, which allows them to adapt to new hosts and ecological niches.<sup>17</sup>

There are four main subgroupings of coronaviruses—alpha, beta, delta, and gamma—that are broadly distributed in mammals and birds, and only alpha and beta are known to cause disease in humans. These viruses cause respiratory, enteric, cardiovascular, and neurological illnesses. Seven coronaviruses with zoonotic origins from bats, mice, or domestic animals have been identified in humans (Table 1.1). Four of the known coronaviruses—229E, OC43, NL63, and HKU1—cause symptoms of the common cold and other respiratory-related symptoms. Two, SARS and MERS coronaviruses, are deadly in humans, and the SARS-CoV-2 is responsible for the COVID-19 pandemic.

SARS was the first human coronavirus to elicit a massive public health response and had a major economic impact in several countries in Asia. Emerging in Guangdong, southern China in November 2002, it spreads to 26 countries, infected 8096 persons, and caused 774 deaths (nearly 10% mortality rate).<sup>18</sup> It was contained through strict quarantine of all infected people and their contacts, and in some areas community-level quarantine.<sup>19</sup> By interrupting human-to-human transmission, SARS disappeared by July 2003 leaving behind an indelible impression on countries in the region.

Ten years later, a second coronavirus, MERS CoV, jumped from bats through its intermediary host, dromedary camel, in Saudi Arabia. Although it remained limited to individuals from the Arabian peninsula or those who had recently returned from the Middle East.<sup>20</sup> There was a major outbreak, lasting 2 months in 2015, in Korea



Structural Protein	Function of Protein
Nucleocapsid Protein (N)	<ul style="list-style-type: none"> <li>Bound to RNA genome to make up nucleocapsid</li> </ul>
Spike Protein (S)	<ul style="list-style-type: none"> <li>Critical for binding of host cell receptors to facilitate entry of host cell</li> </ul>
Envelope Protein (E)	<ul style="list-style-type: none"> <li>Interacts with M to form viral envelope</li> </ul>
Membrane Protein (M)	<ul style="list-style-type: none"> <li>Central organizer of CoV assembly</li> <li>Determines shape of viral envelope</li> </ul>

It has been noted that some CoVs do not need to have the full ensemble of structural proteins to make virions, highlighting that certain proteins may be dispensable or compensated by the function of non-structural proteins.

**Figure 1.2** General structure of coronaviruses. *Source:* Seah I, Su X, Lingam G. Revisiting the dangers of the coronavirus in the ophthalmology practice. *Eye* 2020;34:1155–1157. <https://doi.org/10.1038/s41433-020-0790-7>.

**Table 1.1** Comparison of Origins and Clinical Features of Human Coronaviruses

HCov	Year Identified	Natural Host/ Intermediate Host	Incubation Period	Clinical Symptoms
229E (alpha)	1966	Bats/ camelids	2–5 days	Common cold—headache, sneezing, malaise and sore throat, fever and cough in 10–20%
OC43 (beta)	1967	Rodents/ bovines	2–5 days	Common cold
NL63 (alpha)	2004	Bats/ unidentified	2–4 days	Moderate upper respiratory infection, severe lower respiratory tract infection, croup, and bronchiolitis
HKU1 (beta)	2005	Rodents/ unidentified	2–4 days	Common cold can advance to pneumonia and bronchiolitis
SARS (beta)	2003	Bats/palm civets	2–11 days (median 5 days)	Fever, myalgia, headache, malaise, dry cough, dyspnea, diarrhea, respiratory distress
MERS (beta)	2012	Bats/ dromedary camels	2–13 days	Fever, cough, chills, sore throat, myalgia, arthralgia, dyspnea, pneumonia, diarrhea and vomiting, acute renal impairment
SARS-CoV-2 (beta)	2019	Bats/ pangolins?	3–6 days (5 days)	Fever, dry cough, dyspnea, myalgia, headache, loss of smell and taste, diarrhea

when an infectious traveler subsequently infected five superspreaders.<sup>21</sup> MERS had a very high mortality rate, 34% (857 deaths), and as of January 2020, the total number of confirmed cases was 2519 across 27 countries but the 85% cases were limited to Saudi Arabia.

The most recent coronavirus to make the interspecies jump is SARS-CoV-2. Unlike SARS and MERS, it is a more stealthy virus and can be spread by people who do not display any outward symptoms of the disease but are infectious and expelling virus droplets. In some cases, infected cases are presymptomatic and go on to develop symptoms a few days after exposure. However, an unknown number of infected people never develop any symptoms, remaining asymptomatic who spread the virus (discussed in Chapter 3).<sup>22</sup>

The actual number of infected cases who are asymptomatic ranges widely for COVID-19. On the Diamond Princess cruise ship 17.9% of cases were asymptomatic<sup>23</sup>; on the *Mortimer* (Antarctica cruise ship) 81%<sup>24</sup>; in Iceland 43%<sup>25</sup>; 50–75% in the Italian village of Vo<sup>26</sup>; and an estimated 30% in South Korea (based on a model),<sup>27</sup> but 4% in an actual outbreak.<sup>28</sup> The phenomenon of asymptomatic infections was observed in both SARS and MERS. During the SARS outbreak in Singapore in 2003, 7.5% of health-care workers and 13% of cases in the general population were asymptomatic.<sup>29</sup> In a retrospective data analysis of MERS, an estimated 28.6% of cases were observed as asymptomatic bringing down the case fatality rate (CFR).<sup>30</sup>

Because of asymptomatic cases of infection, the CFR associated with COVID-19 has been difficult to measure and ranges widely from as high as 15.3% in France to as low as 0.1% in Singapore.<sup>31</sup> It is suspected that COVID-19 mortality rate in the general population is greater than the common influenza virus (0.1%), but far less than SARS and the death rate of 2.5% for the Spanish Flu of 1918. The risk of mortality is higher for the elderly (60 years and over) and increases with age, those with comorbidities (such as diabetes, heart disease, among others), those who are immunocompromised, and for males. SARS, MERS, and SARS-CoV-2 exhibit a lot of common characteristics and demonstrate that they are not limited by geography, and far more dangerous in an interconnected and densely populated world (Table 1.2).

## 1.4 Cross-Species Transmission

SARS-CoV-2 and the other recent viruses (such as HIV and Ebola virus) that have jumped from nonhuman to human carriers are examples of species to species migration, with the impact of a species virus on another species not well understood—and they also have the potential to introduce evolutionary changes—mutations—during the jump that could have far more devastating downstream impacts. A pathogen pyramid is useful for understanding successful interspecies virus transmission (host switching) and the emergence of new disease (Figure 1.2).<sup>33, 34</sup>

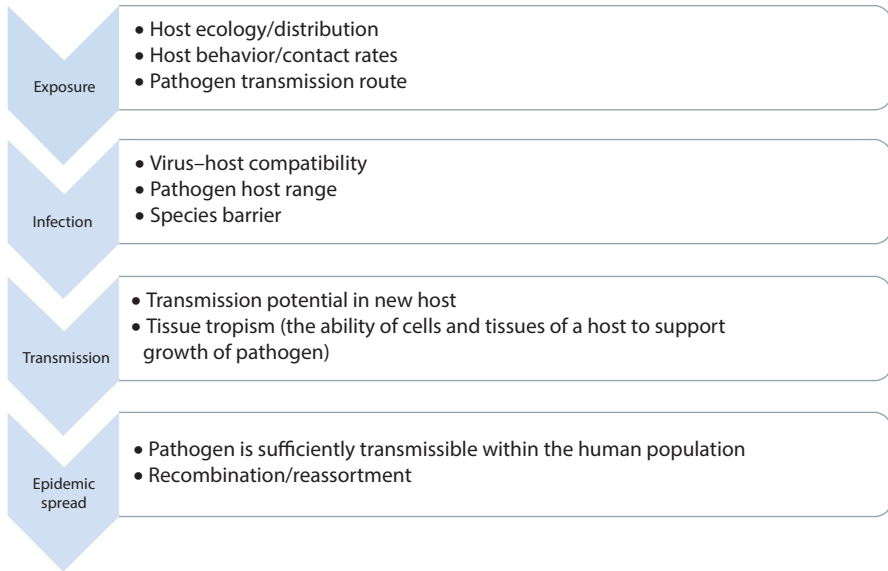
The framework has four levels that are crucial for understanding emerging infectious diseases in humans. The first level is the exposure of humans to new pathogens, which requires contact between people and the host reservoir that can happen because of the changes in human ecology and environment, patterns of agricultural

**Table 1.2** Comparison Between SARS, MERS, and COVID-19: Epidemiological and Clinical Characteristics

Characteristic	SARS	MERS	COVID-19
Dates	November 2002–July 2003	September 2012 till present	December 2019 till present
Incubation period	2–10 (7) days	2–10 (5.5) days	2–14 (5.2) days
Infectious period	Displaying symptoms	Displaying symptoms	Presymptomatic/asymptomatic
Median age of affected individuals (years)	65	50	59
Male/female	Male	Male	Male
Speed of transmission	Moderate	Low	High
Geographic impact	26 countries	27 countries	213 countries (two international conveyances)
Total infections	8,096	2,519 (Jan 2020)	10,008,027 (June 27, 2020)
Total deaths	774	866	499,102
Rate of transmission $R_0$	2.9	3.0 8.1 in Korea outbreak <sup>32</sup>	2.0–2.5

production or domestication of animals, mining, and other such factors. After exposure to pathogens, the pathogen, in the second level, has to possess the ability to infect and cause disease in humans. At the third level, once the pathogen has established its ability to infect humans it has to prove its capacity to transmit the disease to other humans. The pathogens have to effectively exit the body through the upper respiratory tract, lower gut, urogenital tract, skin, or other fluids and infect another human. In the final level of the pathogen pyramid, the pathogen has adapted to the human host without the involvement of the original reservoir and can efficiently transmit such that a single index case is able to generate more than one secondary infection (the  $R$  naught, basic reproductive rate, is greater than one). Pathogens that have worked through these four levels become sufficiently transmissible to cause major outbreaks or to become endemic in human populations.

SARS-CoV-2 has successfully gone through these four levels and exhibits a strong potential of becoming the fifth coronavirus to become endemic in humans. What is notable about this coronavirus is that it has demonstrated successful host switching mechanisms along with effective human-to-human transmission through symptomless but infected cases (Figure 1.3). Thus far, mutations that might make the virus more or less lethal or contagious appear rare and the altered strains appearing in different regions appear to share similar genetic structures.<sup>35</sup>



**Figure 1.3** The pathogen pyramid or steps involved in the emergence of host-switching pathogens. *Source:* Adapted from Refs.<sup>33, 34</sup>

## 1.5 Past Pandemics and COVID-19 in the Context of History

One of the most powerful examples of a global pandemic, the Spanish Flu, occurred in 1918 and is instructive on a number of levels.<sup>36</sup> During its brief run, it infected 500 million people (one-third of the world’s population) and claimed an estimated 50 million lives. Mortality was high in people younger than 5 years and those above 65 years, and also among those between 20 and 40 years, which was a unique feature of the pandemic. Although the Spanish Flu did not originate in Spain and the first case was in the state of Kansas, United States, it was labeled such because Spain having remained neutral during the War had not imposed any censorship. Newspapers were, therefore, free to report on the H1N1 influenza A virus with avian or swine origins.

The virus had multiple, closely spaced pandemic waves between February 1918 and April 1920.<sup>37</sup> The first wave, beginning in March 1918, spreads across the world facilitated by overcrowding, poor sanitation, travel of people to cities in support of the War and soldiers traveling to battlefields, and an immunologically naive population. In this first wave, the disease was relatively mild with symptoms that included high fever and feeling tired lasting around 3 days, but it disrupted the war efforts by causing significant numbers of soldiers to fall sick.

In August 1918, the virus mutated, and the second wave of the disease left a far more deadly footprint. In the mutated version, death occurred within 24 h after disease onset. The disease found a perfect transmission environment among soldiers returning home to their countries and bringing back a more virulent

version that caused, otherwise healthy, patients basically drowning, with their lungs saturated by pneumonia. Later analysis showed that the deaths were not the result of the mutated virus but the patient's own immune reaction, the "cytokine explosion," a protective measure by the body designed to promote healthy inflammation.

The Influenza Pandemic of 1918–1919 occurred at a time when the microscopes did not have the ability to see a virus and very little was known about the microbiology of diseases. It was understood that the human-to-human transmission took place through respiratory droplets. There was no treatment—no antivirals or antibiotics (penicillin would not be discovered until 1928)—and physicians used convalescent sera to reduce the risk of death. Community mitigation strategies relied on nonpharmaceutical interventions including improved hygiene measures, school closures, bans on public gatherings, wearing of face masks, and isolation or quarantine orders.<sup>38</sup> These measures helped to slow down the spread of the virus, and by 1920, the pandemic was over and became a historical event.

The precautionary tale of the 1918 Influenza Pandemic contains a few lessons for the current COVID-19 pandemic which include

- Understanding transmission pathways and implementing measures for slowing down and eliminating the virus.
- Knowing the etiology and physiology critical for treating the disease.
- Protecting the most-at-risk populations versus those that are relatively safe and recognizing that any measures described as exaggerated are probably insufficient.

The current COVID-19 pandemic is a sign of what the world can expect in the future. Even if this current pandemic is not as deadly as the flu of 1918–1919, it will have long-term impacts on health, health services, global economies, social policies, and politics. It has already affected people's financial and job security, and affected everyone at a deep sociological and psychological level. But for all its uniqueness, the pandemic is not likely to remain a one-off, and there may be next waves of pandemic diseases hitting the world. There have already been reports of a new G4 virus, genetically descended<sup>39</sup> from the H1N1 swine flu, with "all the essential hallmarks of a candidate pandemic virus."

Given the immense variability of nature, the fascinating ability of evolution in genetics and finally the almost unlimited number of viral populations waiting to cross from species to species, one thing is clear: there will be other viral attacks and these others will have more dramatic impacts on our population and could lead to far more devastating impacts on society.

The challenge for the global community, and all of its health professionals, is to ensure that all elements of international surveillance systems are enlisted, and that health systems have the ability to quickly identify and classify the nature of the disease and to develop and enforce treatment and prevention models that protect the most vulnerable.

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# Virology and the Immune System Response to COVID-19



Carey Kriz and Syed Imran Ahmad

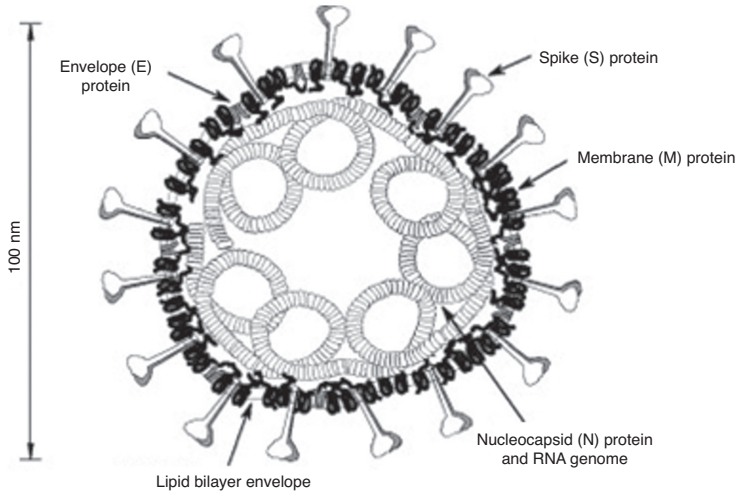
## List of Abbreviations

ACE2	Angiotensin-converting enzyme 2
ARDS	Acute respiratory distress syndrome
ORF	Open reading frames
PRR	Pattern recognition protein
PAMP	Pathogen-associated molecular pattern
RBD	Receptor binding domain
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2

## 2.1 Introduction

In any disease, it is important to understand the structure of the invading pathogen and the immune response of the host. In COVID-19, the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), other systems, in addition to the respiratory system, can be affected. The disease is also unusual in that there is very low prevalence and almost no mortality in children, but the severity of the disease and the risk of mortality appear to increase with age (especially among those aged 70 years and older). Furthermore, the course of COVID-19 is in general more severe in those with underlying conditions or immunosuppressed.

This chapter addresses the immunopathology of SARS-CoV-2 infection. It discusses the structure of the virus, presents an overview of the innate and adaptive immune system, and describes the changes occurring in the bodies of COVID-19 patients, particularly the dysregulation of the host immune system reflected by the cytokine storm. This chapter provides an understanding of the immune system mechanisms that can help with the clinical management of COVID-19 cases.



**Figure 2.1** Structure of SARS-CoV-2 responsible for COVID-19.

## 2.2 SARS-CoV-2 Structure

Coronaviruses have the largest genome of all RNA viruses and are classified within the order Nidovirales.<sup>1</sup> The SARS-CoV-2 is the seventh identified coronavirus and in the same beta-coronavirus clade as SARS-CoV and MERS-CoV, sharing almost 80% of the genome with SARS-CoV.<sup>2</sup> Similar to other coronaviruses, SARS-CoV-2 contains a single-stranded RNA genome covered with a protein membrane and protein spikes (S) on its surface (Figure 2.1). The S surface protein plays key roles in the viral life cycle and host defense response. The glycoprotein of these protein spikes has a unique way of binding with the cell membrane protein, angiotensin-converting enzyme 2 (ACE2), on the surface of host cells. ACE2 host receptor is required for the host cell entry of SARS-CoV-2, and their expression is not only restricted to the lungs but also to other systems in the human host.<sup>3</sup>

The entry of SARS-CoV-2 requires conformational changes to the S protein. The serine protease called furin cleaves the S protein and is essential for the fusion of the viral and host cell membranes and viral entry to the cell through endocytosis or nonendocytic cell surface entry.<sup>2,4</sup> The S protein contains a S1 component, a surface subunit that binds to the host cellular membrane, and a S2 component, a transmembrane subunit that allows for fusion. Cleavage at different sites on the S protein not just increase fusion, but also accelerate cell-to-cell spread. Due to its critical role in infection, furin is a possible target for therapeutic interventions.<sup>5</sup> In the endocytic pathway (potential targets of drugs such as chloroquine and hydroxychloroquine), the virion fuses with the vesicle and releases its single-segmented RNA genome into the cytosol for immediate replication.

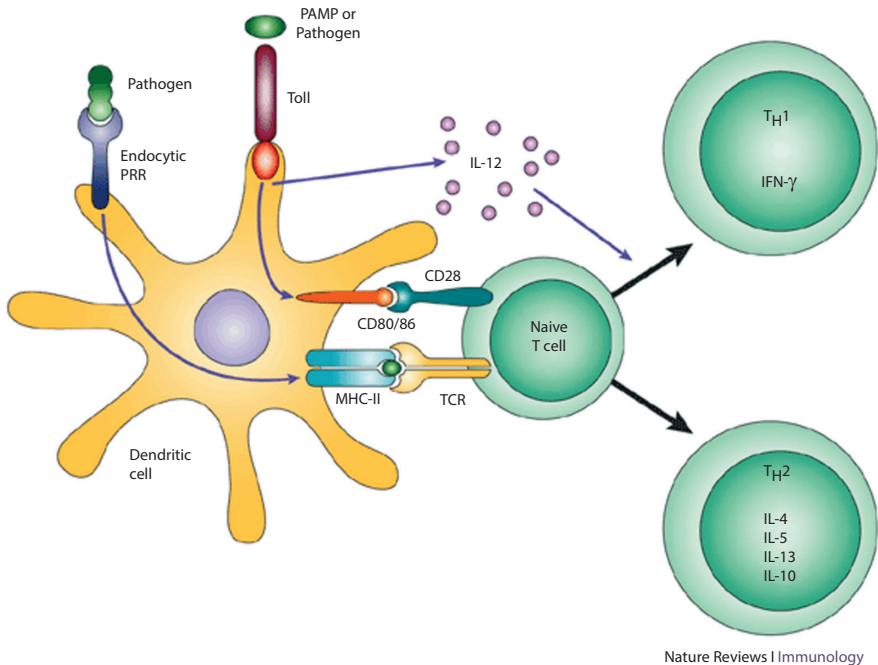
SARS-CoV-2 infection activates innate and adaptive immune responses, which are described in the next section.

### 2.3 The Immune System

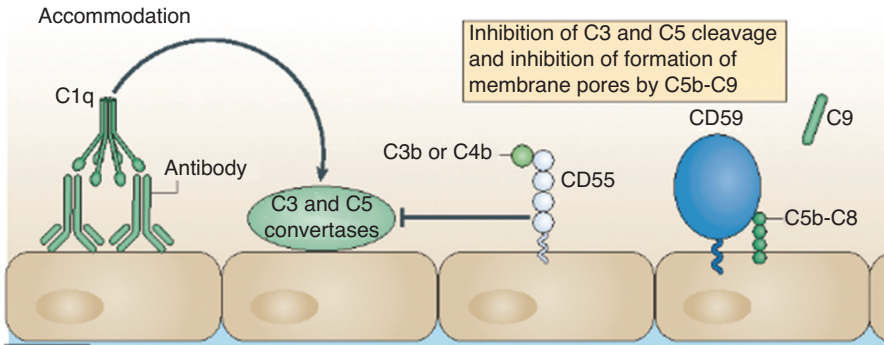
The body’s response to SARS-COV-2 has foundations deeply rooted in our immune system, and thus, a brief review of the basics is essential. The immune system is complex and involves a network of players that interact with each other. An invading pathogen triggers the innate immune response. While many infections can be dealt through this innate system, humans also have an additional layer of defense, the adaptive immune system that actually adapts to protect against specific invaders. Both aspects of the immune system are described below.

#### 2.3.1 Innate Immunity

The first line of defense mechanism against foreign microorganisms in humans is mediated by the innate immune system. The key cells in the inflammatory process include neutrophils, macrophages, dendritic cells, and natural killer (NK) cells.<sup>6</sup> These cells utilize mechanisms like cellular recognition proteins to identify foreign cells and remove them from the body (Figure 2.2).



**Figure 2.2** Basic function of innate immunity showcasing the interaction of antigens with toll-like receptors on macrophages. This figure also illustrates the interface between innate and adaptive immune systems.<sup>6</sup>



**Figure 2.3** Function of complement response in innate immunity.

Pattern recognition proteins (PRRs) are the essential component of innate immunity. Neutrophils and macrophages have protein receptors on their cell membranes that recognize certain “patterns” on foreign cells and not only recognize them as foreign, but also differentiate them from host cells during elimination. Examples of pathogen-associated molecular patterns (PAMPs) are bacterial endotoxins in gram-negative bacteria, peptidoglycans, lipoteichoic acid, and viral double-stranded RNA (Figure 2.3).<sup>5</sup>

One of the most important and well-studied examples of PRRs is the complement system, a series of circulating peptides that play a crucial role in innate host immunity. A major component of this system, the C1 protein, recognizes antibodies bound to microbial proteins and initiates a downstream event, known as the complement cascade.<sup>7</sup> The result of this event is the production of C3b that leads to chemotaxis, opsonization, and phagocytosis of bacteria, and to the formation of membrane attack complex. Another type of PRR is the toll-like receptor, which is a transmembrane protein found on neutrophils and macrophages that binds PAMPs and results in the transcription of inflammatory genes, leading to inflammation.

The key players of the innate immune system are the neutrophil, macrophage, and NK cells. Neutrophils are directed to the sites of inflammation or infection by cytokines such as IL-8 and C3b proteins. Macrophages serve a similar function, but they respond somewhat slower than neutrophils. NK cells contain similar protein receptors, which are used to differentiate between host and infected/injured cells. Once recognized, NK cells induce apoptosis. NK cells are especially important in protection from viruses and tumor cells. Other important components of the innate immune system are eosinophils, basophils, and mast cells.

An important point about the innate immunity system is that it does not contain memory cells or “learned responses” to a specific antigen. The innate immune system is general and nonspecific to inflammation. Unlike the adaptive immune system that fine-tunes and modifies itself to combat a specific infection/injury over a longer period, innate immunity is designed to respond immediately. Innate immunity, however, is the preliminary process that is needed to generate the adaptive immune system.

## 2.3.2 Adaptive Immunity

Unlike the innate immune system, the adaptive immunity system is a more refined and calculated mechanism of host defense. The mounted response of the adaptive immunity takes place over a longer period of time compared to the more generalized instantaneous response of the innate immune system. This section will briefly discuss two types of Adaptive immune responses: Humoral immunity and Cell-mediated Immunity.

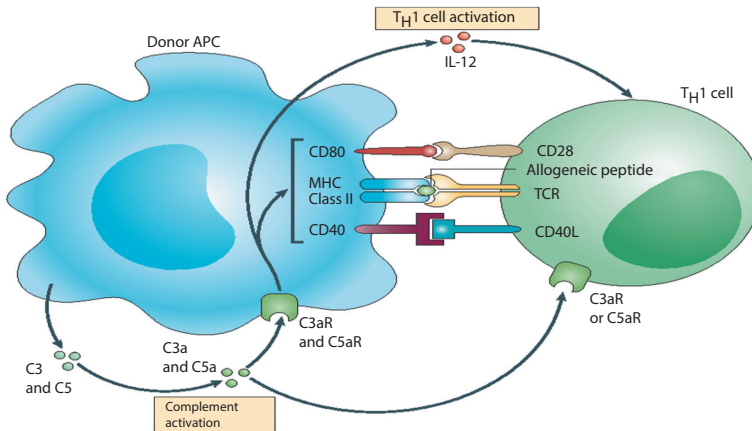
### 2.3.2.1 Humoral immunity

Humoral immunity is driven by B-cells that secrete antibodies to protect the body from immediate- and long-term foreign microorganisms. The cardinal event involves receptors on B-cells binding to an antigen.<sup>3</sup> This binding promotes activation and differentiation into more specialized cells. The B-cells consist of a B-cell receptor, which is made up of light and heavy immunoglobulin chains, and B-cell co-receptor, which is required for proper antigen binding. Binding of antigens on multiple B-cell receptors leads to a series of intracellular phosphorylation via the IP3 and diacylglycerol (DAG) pathways, intracellular signaling, which results in the translocation of transcription factors to the nucleus and activation of B-cells.<sup>8</sup>

B-cells can now bind to thymus-dependent and thymus-independent antigens. The classic examples of thymus-independent antigens are the polysaccharides on capsular organisms such as *H. influenzae* and *S. pneumonia*, which leads to our body mounting an antibody response. This mechanism is also the basis for the unconjugated polysaccharide vaccinations. These capsules contain sugar and are not suited for a more robust T-cell-mediated vaccine response. However, B-cells are the ideal candidates for responding to these foreign pathogens.

Thymus-dependent antigen leads to a specialization of B-cells into assuming more specific roles. Binding of these antigens primes T-helper cells. These T-cells then activate B-cells into secreting specific types of antibodies. For example, in the germinal centers of secondary lymphoid tissue, binding of antigen-carrying B-cells to a Th2 cell and its co-receptor leads to the release of IL-4 and IL-5, which signals B-cells to secrete IgE. IgE antibodies then protect against helminthic infections and mediated atopic diseases. This process is called class switching and facilitated by somatic mutations in the heavy chain regions of immunoglobulins. IgM antibody-secreting generalized B-cells differentiate into serving more specific roles.

This is a brief summary of how B-cells work, and the process is an arduous one. Within the germinal centers of lymphoid tissue, each individual B-cell is faced with essential tasks for it to survive and proliferate. These tasks include competing with other B-cells for binding antigens, processing the antigens, and presenting them to T-helper cells on their MHC-II (proteins that present exogenous antigens), receiving stimulating signals from co-receptors, and then finally specializing. Highly specialized and differentiated B-cells can also circulate in the plasma as memory B-cells where they “remember” the antigens they once interacted with and can class switch into secreting antibodies.



**Figure 2.4** Activation of Th1 cells.

B-cells also play a crucial role in innate immunity. As we discussed above, the complement system is a key component of the innate immunity.<sup>7</sup> Antigen bound to Fab regions of IgG antibodies get cross-linked to Fc regions of antibodies. Essentially, the antibody serves as a bridge for complement and antigen. Once the bridge is formed, complement can implement the recruitment of neutrophils and eventual phagocytosis of the microbe.

### 2.3.2.2 Cell-mediated immunity

Cell-mediated immunity is a vigorous system of host defense mechanisms that is designed to combat intracellular microbes such as viruses and mycobacteria along with tumor cells. The same system is also the culprit behind many autoimmune conditions. T-cells are the primary driver of cell-mediated immunity. Although there are several types of T-cells, CD4 and CD8 cells, expressed by the cytotoxic T lymphocytes, are important in measuring immunity of the patients (Figure 2.4).<sup>6</sup>

CD8+ cells are cytotoxic cells that have cytotoxic mechanisms against infected cells by which after binding, it causes a fusion and release of granules that lead to cellular damage. CD8+ cells also express a Fas ligand that binds to CD-95 receptors on infected cells.<sup>6</sup> The binding leads to apoptosis. CD8+ cells take things into their own hands and eliminate virally infected and tumor cells via apoptosis or involvement of NK cells. CD8+ cells must be activated via antigen presentation through the MHC-1 class of cells. Since all nucleated cells in the body express MHC-1, CD8+ cells are ideal for eliminating cells that may be infected by viruses since any cells can present antigens to CD8+ cells. However, before CD8+ cells can acquire this ability, they must be activated in lymphoid tissue with the help of CD4+ cells and antigen-presenting T-cells.

CD4+ cells are the helper T-cells and are activated in lymph nodes when dendritic cells capture foreign antigens and present into T-cells. The binding of T-cell

receptors with these antigen-presenting cells must be accompanied with co-signal binding with the CD-40L on CD+4 cells for the effect to take place. It is also important to mention that these antigens tend to be peptide-based and also form the basis for peptide-based vaccines, like vaccines for diphtheria.

The interaction of CD+4 cells with antigen determines the fate of these T-cells. Cytokines or cellular messengers drive this differentiation. Through events in the innate immunity, IL-12 and interferon gamma are produced, which induce CD+4 T-cells conversion into Th1 cells.<sup>6</sup> These cells then secrete more IL-12 and IFN gamma, which promotes class switching of B-cells into secreting IgG and also activates macrophages. Macrophages are activated by the release of IL-12 and IFN gamma from Th-1 cells. In other words, it becomes a self-regulating cycle. Naive CD+4 cells get converted into Th-1 cells by certain cytokines. Th-1 cells then secrete cytokines of their own, which prepares a robust immune response, resulting in a proinflammatory condition that plays an essential role in eradication of the virus.

A classic example of this pathway is our body's response to primary tuberculosis. As mentioned in the section for humoral immunity, if naive CD+4 cells are met with other stimuli, they can differentiate into Th-2 cells, which play a role in atopy and protection against parasitic infections. Other types of specialized helper T-cells are regulatory T-cells, Th-17 cells, and follicular helper T-cells.

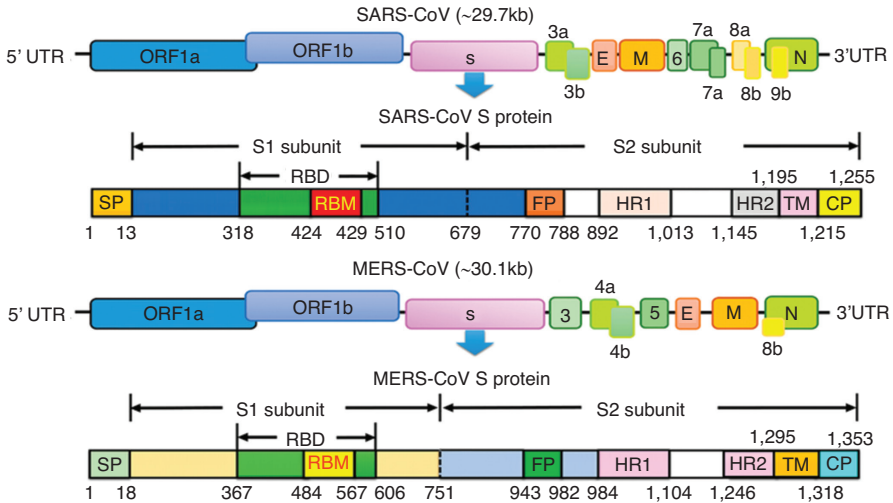
Cell-mediated immunity also displays the phenomenon of memory cells. Interactions with antigens induce changes in surface molecules and intracellular mechanisms which allows T-cells to mount a more rapid and specialized response if exposed to the same antigen again. In other words, T-cells remember antigens they once battled again and know exactly how to defeat them if they return. This forms the basis of life-long immunity and is the reason behind how vaccines work.

Although this discussion is brief, a more detailed study of the immune system can be found in textbooks dedicated entirely to it. These sections are a quick framework review of how our body's defense systems work that can be quickly accessed and referenced when trying to make sense of our body's response to the SARS-CoV-2 pathologies.

## 2.4 Pathophysiology of SARS-CoV-2

The virulence of SARS-Cov-2 virus is attributed to its structural proteins that allow it to enter the human body and replicate. Hence, the genomic activity and replication are essential to its pathogenicity. The SARS-CoV-2 virus is a positive sense, single-stranded RNA virus with a 5'cap and 3' polyA tail.<sup>9,10</sup> Transcription of the virus occurs between open reading frames (ORFs) found on the RNA. Up to 6 ORFs can be present in a replication-transcription complex (RCT).<sup>11</sup> The result of this transcription is a set of structural proteins, envelope proteins, spike proteins, and nucleocapsids. Frameshift mutations between these ORFs can lead to new and different types of proteins, increasing the pathogenicity (Figure 2.5).





**Figure 2.5** Genomic structure of the SARS-CoV and MERS-CoV, depicting the ORF regions found in the SARS-CoV Virus.<sup>9</sup>

### 2.4.1 Interaction between SARS-CoV-2 and ACE2

The interaction between surface glycoprotein or “spike protein” on virions and human ACE2 enzymes starts the inflammatory process. Of note is that the quantity of enzyme may be related to the extent of organ inflammation.<sup>8,12</sup> For example, ACE2 is found in the pulmonary capillaries, and development of COVID-19-induced pneumonia and acute respiratory distress syndrome (ARDS) is a common cause of mortality.<sup>13</sup> The enterocytes and epithelia of the gastrointestinal tract also contain ACE2 and can be attributed to the gastrointestinal (GI) symptoms of SARS-CoV-2.<sup>14</sup> Though it is now known that the virion can cross the blood–brain barrier, neurological symptoms such as anosmia, nausea, and headaches are linked to the presence of ACE2 in the brain. Another crucial organ system that is host to ACE2 enzymes is the myocardium. High expression of the enzyme in the heart increases the chance of infection.<sup>12</sup> It is possible that infection leads to thrombosis and vasoconstriction of the vasculature in the myocardium. Hence, the incidence of thrombosis in intensive care unit (ICU) patients infected with COVID-19 is 31%.<sup>15</sup>

### 2.4.2 Pathogenesis and Biochemistry

SARS-CoV-2 is structurally similar to the original SARS virus responsible for the 2002–2003 outbreak. Studies have shown that both of these viruses share a similar spike glycoprotein structure in the receptor-binding domain (RBD) that is responsible for their affinity for the ACE2. Specifically, the 3D structure of the spike protein on both of these viruses is identical. Furthermore, the amino acids in the whole

protein that comprise these RBDs are homologous in both of these viruses while also sharing 76–78% of the same amino acid sequences.<sup>10</sup> explored this likeness. The affinity between the RBD on viral cells to host ACE2 cells is crucial in pathogenicity. The virion infects the cell by attaching its glycoprotein into host cell receptors, leading to fusion and insertion of viral replication components into the host. Molecular analysis of crystal structures containing RBD–ACE2 complexes isolated from different hosts and identified certain amino acid residues on ACE2 that increased the affinity for binding with the viral glycoprotein.<sup>1</sup> The RBD sequence on SARS-COV-2 that interacts with the ACE2 is very similar to the original SARS virus, showcasing why SARS-CoV-2 enters the human body through the ACE2 cells. Furthermore, the sequence also showed similar receptor binding motifs on the 2019 virus with high affinity for the amino acid residues on ACE2 cells. In other words, ACE2 is required for viral entry and further replication.

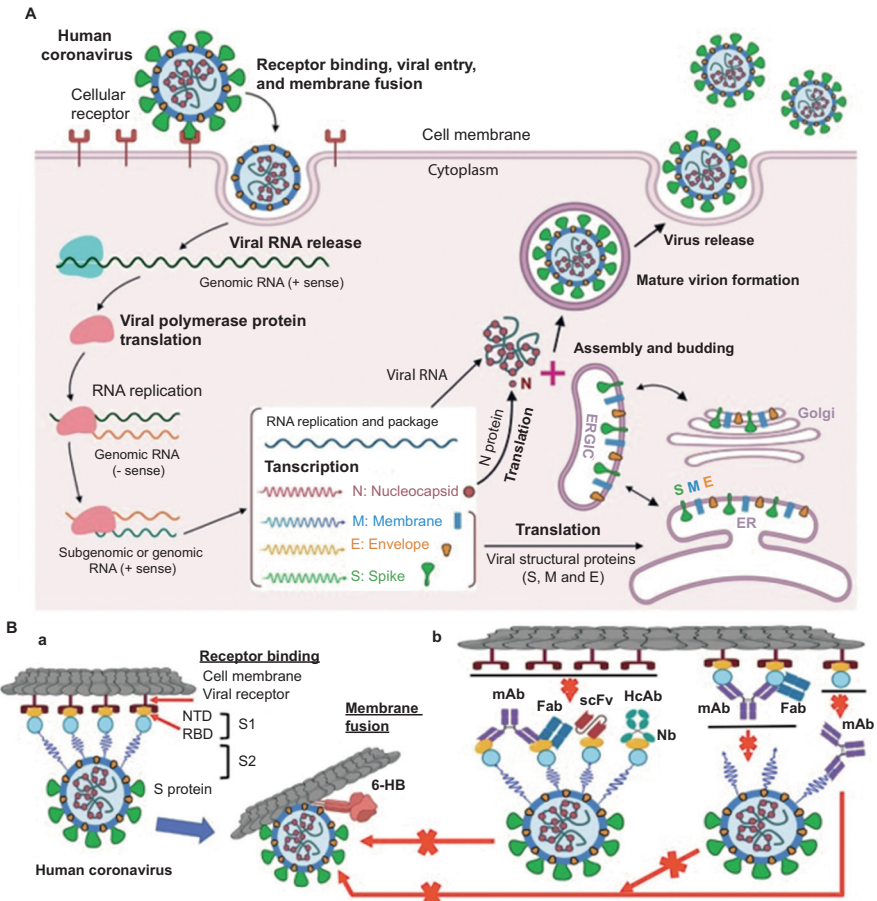
The surge of ICU cases and respiratory failure all over the country has demonstrated that lung-related mortality is a key feature of SARS-COV-2. This interaction between the virions and the ACE2 is strongly linked to the severe ARDS and pneumonias. We will discuss a few studies in the following section to better analyze the relationship between how viral protein binding with ACE2 receptors affects the respiratory system (Figure 2.6).

### 2.4.3 Pathophysiology of COVID-19-Related Organ System Involvement

Understanding the role of ACE-2 and pathogenesis of SARS paves the way for explaining why SARS-CoV-2 is so destructive to the lungs. SARS-COV 1 was suggested to have an affinity for respiratory infection through ACE-2 in a 2005 study titled *A crucial role of Angiotensin Converting Enzyme 2 (ACE2) in SARS-coronavirus induced lung injur*]. In their research, Kuba et al. infected two groups of mice with the SARS-CoV-2: the control group wild type expressing ACE2 and an experimental group with ACE2 knocked out. They later isolated a much smaller number of infectious viruses from the experimental group, indicating a decreased lung pathogenicity.<sup>15</sup>

The study titled *Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan COVID-19* further analyzed the connection between COVID-19 and lung pathogenicity. Zhao et al. studied healthy pulmonary parenchyma from eight donors and found that ACE2 is expressed in 83% of type II alveolar epithelial cells. Gene ontology analysis has revealed that these type II alveolar cells also contain genes that somehow promote viral replication and ensure its survival. Though evidence on this phenomenon is inconclusive.<sup>11</sup>

Introduction of viral particles and its life cycle in the large surface area of the lungs may be the reason behind cases of pneumonia, ARDS, and diffuse alveolar damage. Parenchymal involvement causes acute lung injury and the release of pro-inflammatory cytokines such as IL-8, TNF, and IL-6, activating the innate immune system, as discussed above, and leading to the recruitment of neutrophils and



**Figure 2.6** The life cycle of the human coronavirus, depicting cellular entry and subsequent replication.

macrophages to the site of infection at the pulmonary capillary epithelium.<sup>13</sup> Neutrophil-mediated injury of the capillary epithelium leads to the leakage of fluids and protein to the alveoli causing a state of pulmonary edema. Subsequent development of ARDS becomes imminent, causing an impairment of gas exchange and pulmonary compliance. Depending on the severity of the inflammation, oxygenation and worse intubation may become a necessity. This feared chain of events is often the culprit behind SARS-CoV-2-associated mortality.

Examining evidence, we can see that acute lung injury and ARDS progress rapidly. One study examined 138 hospitalized patients for pneumonia, of which 20% developed ARDS within 8 median days and 12% required mechanical ventilation. A different study from Wuhan showed ARDS in 41% of hospitalized patients from pneumonia.<sup>15</sup> What exactly is causing the rapidly worsening respiratory failure? One possible speculation can point towards the idea that the large surface area of

lungs with type II alveolar cells are invaded by the virus, leading to immune response and subsequent development of ARDS.

Systemic hyperinflammation is another culprit that plays a role in progressively worsening ARDS and may play a role in SARS-CoV-2-induced respiratory failure. Studies have shown that early increase in pro-inflammatory cytokines worsens the prognosis of ARDS and pneumonia.<sup>16,17,4</sup> The lymphocytic infiltrates in the systemic inflammation deposit in the lungs and worsen the ARDS.

Historically, the original SARS-COV and MERS-COV both demonstrated increased concentration of pro-inflammatory cytokines such as IL-6, IL-12, and IFN-gamma.<sup>7</sup> Not surprisingly, SARS-CoV-2 has shown similar findings. Furthermore, the quantity of these pro-inflammatory cytokines is higher in patients requiring intubation than in those who did not require mechanical ventilation. Could cytokine-induced inflammation be playing a role in this? The information is currently still under scrutiny. To complicate the discussion even more, SARS-CoV-2 patients have also shown elevated levels of TH-2 helper T-cells which secrete IL-10, an anti-inflammatory cytokine. Therefore, the role of cell-mediated immunity is unclear in the pathophysiology of the infection. Nonetheless, an in-depth exploration of cytokine release syndrome is warranted.

Cytokine-release syndrome (CRS) is a dysregulated pro-inflammatory condition where a positive cycle of cytokine release is established leading to systemic shock and multisystem organ failure. As a response to bacterial and viral infections, the mechanisms discussed in the immunology section allow cell messengers of the innate immunity release cytokines that recruit monocytes and lymphocytes and reinforce the response to eradicate the infection. In most scenarios, especially SARS-CoV-2, this response is sufficient to fight the infection and the host makes recovery. However, failure to eradicate the infection leads to a sustained inflammatory state, where the cytokines exert a positive feedback on the immune cells, which further secrete cytokines, thus creating a cycle. The prolonged immune response then becomes detrimental to the host as systemic vasodilation develops leading to shock and organ failure.

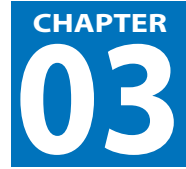
To further this discussion, we will include a hematologic perspective into understanding how coagulation plays a role into SARS-CoV-2-related systemic inflammation. It is well understood that inflammation can activate the coagulation cascade by several mechanics: down-regulation of antithrombin III and other anticoagulant mechanisms, tissue factor-mediated thrombin generation, and impaired fibrinolysis. Thrombin itself is known to induce IL-6 and IL-8 in endothelial cells, which plays a role in the sustenance of inflammation. Furthermore, the endothelial injury induced by pro-inflammatory cytokines worsens the coagulation balance.

This may be the possible basis for cases of disseminated intravascular coagulation (DIC), a condition in which blood clots form throughout the body, and thrombosis seen in severe COVID-19 patients. In the study titled *Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia*, it was found that a large majority of non-survivors met signs of DIC and had significantly higher D-dimer levels, Fibrin degradation products, and elevated PT/PTT. It is thus essential to realize that systemic inflammation and the coagulation system in combination can play a crucial role in overall mortality associated with SARS-COV-2.

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# Transmission, Prevention, and Risk Factors of COVID-19



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## List of Abbreviations

BMI	Body mass index
NPI	Nonpharmaceutical public health intervention
SARS-CoV-2	Severe acute respiratory syndrome coronavirus
SSE	Super-spreader event
TB	Tuberculosis

### 3.1 Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a respiratory virus that spreads from person-to-person through close contact and causes COVID-19. It is highly contagious. Infected individuals who show no symptoms can transmit the virus without knowing they are infectious, making it difficult to control community spread. Although all age groups can be infected, those over 60 years old, specifically males, and those with underlying chronic conditions such as diabetes, pulmonary or heart disease, obesity, or in an immunocompromised state are at higher risk. Until there is a vaccine, COVID-19 prevention will depend on traditional epidemic control measures. This chapter summarizes the latest information on what is known about COVID-19 transmission, prevention, and risk factors.

### 3.2 Viral Transmission

Previous studies of SARS-CoV indicated a significant role of airborne transmission with the virus remaining infectious in aerosol for hours and on surfaces for up to 2 days.<sup>1</sup> Considering that the genome of SARS-CoV-2 is similar to SARS-CoV, the transmission behavior is also more similar. Studies have shown that infected individuals can transmit SARS-CoV-2 through large droplets ( $>5\text{--}10\ \mu\text{m}$ )<sup>2</sup>, and more

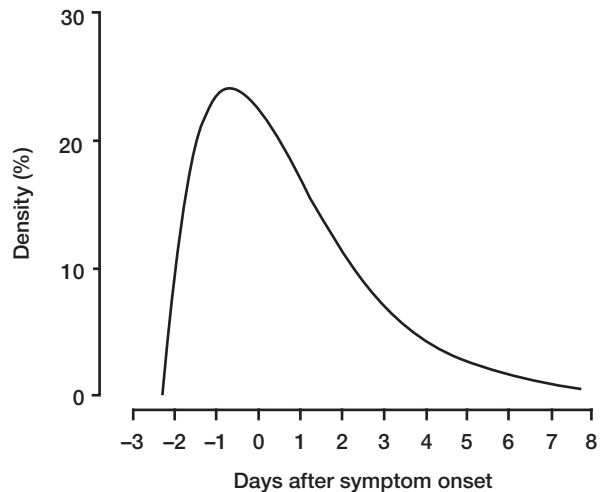
recently through aerosol ( $\leq 5 \mu\text{m}$ )<sup>3</sup> exhaled during breathing, speaking, coughing, sneezing, or yelling. The case study of COVID-19 infections on the cruise ship *Diamond Princess* demonstrated that aerosol transmission contributed to disease progression. The virus is more easily spread in indoor or enclosed environments that have poor or inadequate ventilation.

Viral transmission can also occur through direct contact with an infected person or indirect contact through hand-mediated transfer from contaminated surfaces and objects to the mouth, nose, or eyes. The virus has been detected in various bodily fluids and in feces, but so far there is no evidence of its transmission through these modalities has been found. It is recommended that strict precautions should be taken in hospital settings.<sup>4</sup>

Person-to-person transmission is also dependent on the infectiousness of cases, which is based on the viral load. The viral load is defined as the concentration of viral particles in the biological medium of transmission. The higher the viral load, then it is more likely an infected person will transmit the virus to others. In the case of COVID-19, the viral load is related to the time course of the illness.<sup>5</sup>

The incubation period, which is the time between exposure to the virus and symptom onset, for COVID-19 is 4–5 days, and in some cases, it can be up to 14 days. In Figure 3.1, the  $y$ -axis represents the viral load, and the  $x$ -axis represents the days after symptom onset with the first day of symptoms designated as 0. During this time, the viral load gradually rises, peaking about 2–3 days prior to the onset of symptoms. In mild cases, the viral load sharply declines over the course of 7 days such that by the fourth to seventh day of symptomatic infection, the patient becomes much less likely to infect others.<sup>6</sup> In more severe cases, the viral load begins to decline after the second week.<sup>7</sup> But prolonged viral shedding has been reported for up to 63 days in nasopharyngeal swabs among adult patients.<sup>8</sup>

**Figure 3.1** Viral load density of COVID-19.<sup>5</sup>



In terms of transmission, few concerns are the presymptomatic or asymptomatic cases, transmitting the disease few days *before* the onset of symptoms when the viral load is highest without being aware that they are infecting others.<sup>9</sup> The role of asymptomatic cases in transmission, while reported, has been difficult to quantify.<sup>10</sup> But the risk of transmission from presymptomatic cases is high, and according to some reports contributed to 48% and 62% of transmissions in Singapore and China.<sup>11</sup> It is safe to assume that a significant proportion of secondary transmission is occurring before the onset of illness and, in some instances, in the absence of symptoms.

A comparison of SARS-CoV-2 to SARS displays the immense power of transmissibility of this virus since it can be spread by presymptomatic and asymptomatic individuals through airborne transmission and requires greater individual and community vigilance. In contrast, SARS differed in the sense that affected patients became symptomatic soon after infection and could be easily isolated. As a result, SARS was successfully contained using old-style public health measures such as isolation and quarantine.

### 3.3 Reproductive Rate and Dispersion

R-naught ( $R_0$ ) is an important epidemiological concept for understanding disease transmission, defined as the average number of new cases generated by every infected case.<sup>12</sup> It is not a fixed value and depends on a variety of factors such as the host's population susceptibility to infection, demographics, socioeconomic situation, and seasonality.  $R_0$  is a useful public health measure in terms of disease spread and its eventual containment. Typically the  $R_0$  value varies between less than 1 if the disease is controlled and greater than 1 if it is spreading. Throughout the course of an outbreak of disease, interventions aimed at controlling the spread can be described as attempts to lower the value of  $R_0$ . The average  $R_0$  of COVID-19 is estimated at the range between 2.2 and 2.7 with a doubling time of cases in 6–7 days.<sup>13</sup>

Since  $R_0$  is an average value, its meaning can be obscured by a highly dispersed distribution where a handful of infected people are causing most of the secondary transmission. The dispersion factor,  $k$ , describes how much a disease clusters through super-spreader events (SSE). A small dispersion factor means that a relatively small number of cases are responsible for transmission, while a larger  $k$  indicates that transmission is more evenly spread.

In the case of COVID-19, a small fraction (10%) of infected individuals is estimated to be causing 80% of the secondary infections through SSE.<sup>14</sup> In many instances, a single infected person transmits the virus to a large number of people while attending large gathering such as meetings, conferences, religious services, sporting events, or other social get-togethers. Large disease clusters have occurred in meetings, nursing homes, churches, prisons, food processing plants, and on



ships.<sup>15</sup> Two other factors affecting clusters of disease outbreak are time and physical space. The longer the period of exposure the group staying together, the likelihood of viral spread is greater. Indoor and poorly ventilated spaces are especially conducive to transmission. In one study from Japan, the odds of transmission in a closed environment were estimated to be 18.7 times greater compared to an open air environment.<sup>16</sup>

### 3.4 Assessing Risk of Transmission

Understanding the risk of infection is important for beating back the virus, and professor Erin Bromage<sup>17</sup> from the University of Massachusetts Dartmouth has developed an easy formula: Successful Infection = Exposure to Virus Volume × Exposure Time (Table 3.1). Some places of high risk usually will have high volumes of viral particles or low volumes of virus but require extended exposure. A massive outbreak was reported in a German slaughterhouse where the virus spreads up to 8 m (26 ft) through the ventilation (air cooling) system infecting 1500 out of 7000 employees.<sup>18</sup>

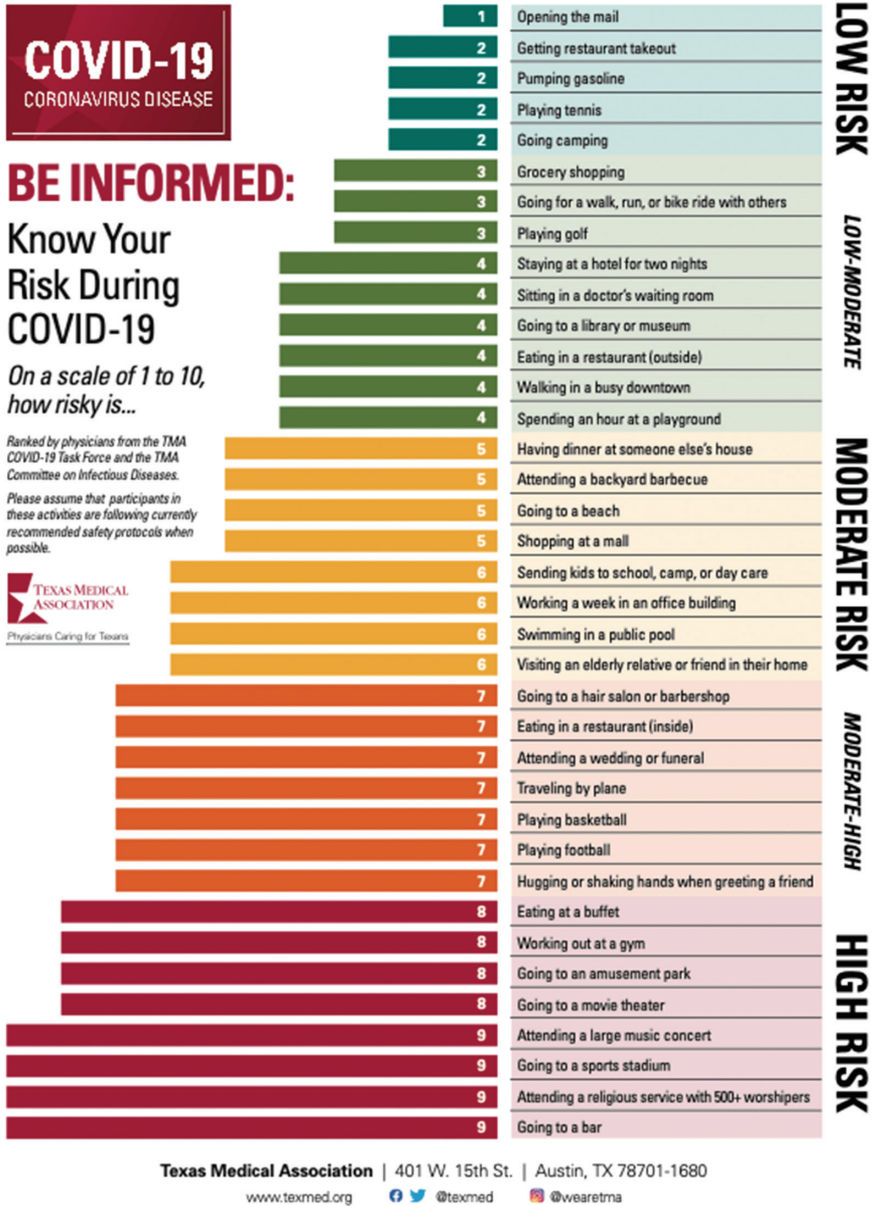
The Texas Medical Association has also developed a risk chart for COVID-19 (Figure 3.2).<sup>19</sup>

### 3.5 Individual Disease Prevention

As an airborne virus, SARS-CoV-2 spreads very easily as demonstrated by a fluid dynamic professor at the Massachusetts Institute of Technology who showed that a turbulent gas cloud created by a cough could reach up to 7–8 m (23–27 ft).<sup>20</sup> In combination with the improved hygiene measures such as regular handwashing and coughing into the elbows, it is also very important to wear facemasks and physically distance from other people. The World Health Organization (WHO) has defined

**Table 3.1** Risk of Transmission: Time and Volume of Virus

	Low Volume	High Volume
Long time	Work place Cruise ship Shopping malls Amusement parks	Restaurants/bars Weddings/funerals/birthdays Concerts Meetings Sports events Meat packing plants Prisons Assisted living housing
Short time	Safe Supermarket Outdoors—jogging/ walking	Public toilets Choir practice Gyms



**Figure 3.2** Risk of COVID-19 infection in a variety of situations.

close contact as being within 1 m (3 ft) of a COVID-19 infected person for more than 15 min while not wearing a mask.<sup>21</sup> In such instances, the recommendation is to quarantine for 14 days, regularly take temperature and monitor symptoms, and to keep a safe distance for other members of the household. The use of facemasks is

recommended during isolation procedures. Only after 14 days or 10 days after the onset of symptoms and two negative tests can a patient come out of quarantine once the symptoms have been cleared.<sup>22</sup>

In addition to preventative measures such as handwashing, coughing into the elbows, wearing a mask, keeping a distance of 6 ft apart from others outside the home, and avoiding large gatherings, there are other steps that should be taken to keep the immune system strong. These include the following:

- Eating a well-rounded and balanced diet that includes whole grains, fruits, vegetables, beans, nuts, and legumes. Some studies have indicated that Vitamin D<sup>23</sup> and zinc<sup>24</sup> may reduce the risk of COVID-19, but these protections are not definitive.
- Exercising regularly as it confers a range of benefits including reducing stress and improving cardiorespiratory fitness.<sup>25</sup> The United States Centers for Disease Control (CDC) recommends 30 min of moderate intensity aerobic exercise 5 days a week for adults, and 60 min of exercise daily for children and adolescents.<sup>26</sup>
- Refraining from smoking<sup>27</sup> as it is associated with increased severity of disease and deaths in hospitalized patients.
- Refraining from alcohol use as it has been shown to increase the likelihood of acute respiratory distress syndrome and liver damage.<sup>28</sup> A study from Wuhan reported that 53% of patients with COVID-19 experienced liver damage as consequences of the infection.<sup>29</sup>
- Sleeping for at least 8 h, which is an essential component for stronger immunity.

The WHO publishes updated guidelines and posters for downloading on how to protect yourself and others against COVID-19 which is accessible at <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public>. Cleaning hands with soap or alcohol-based sanitizers is the most effective way to kill the virus.

### **3.6 Community Prevention: Nonpharmaceutical Interventions**

In situations where vaccines and antiviral agents are insufficient or unavailable, the WHO recommended introducing nonpharmaceutical public health interventions (NPIs) to contain infection, delay spread, and reduce the impact of pandemic diseases.<sup>30, 31</sup> The NPIs are considered outside of health-care settings and focus on measures that (1) limit international spread of the virus (e.g., travel screening and restrictions); (2) reduce spread within national and local populations (e.g., testing, isolation and treatment of positive cases, monitoring and quarantining of exposed persons, and introducing social distancing measures); (3) reduce an individual person's risk of infection; and (4) communicate risk to the public.

In addition to testing and isolating positive cases, contact tracing, and quarantine measures, governments are recommended to introduce NPI measures to control the spread of infection. Nonpharmaceutical interventions include and are not limited to the following:

1. Universal masking mandate in public areas;
2. Maintaining safe distances between people in public spaces;
3. Banning public events and large gatherings that generate crowds, including personal responsibility to limit social gatherings;
4. Closing schools and universities;
5. Closing nonessential businesses;
6. Stay at home orders.

For COVID-19, countries around the world implemented aggressive public health measures to control viral spread. Some countries were successful in bringing down the  $R_0$  including China where the coronavirus originated. A study<sup>32</sup> of the outbreak in Wuhan, the epicenter of the virus, measured the attack rate without any interventions, and after public health interventions were imposed found that the viral attack rate dropped precipitously (Table 3.2). The interventions were estimated to prevent 94.5% of infections.

Although the outbreak started in early December, no strong interventions were implemented until January 20 when human-to-human transmission was confirmed. On January 23, the government imposed an unprecedented policy of *cordon sanitaire* effectively cutting off the city and Hubei province from the rest of the world, but new cases continued to overwhelm hospitals that faced shortages in supply and were understaffed. The rate of viral infection among health-care workers was high probably due to lower awareness of nosocomial infections. The authors observed that asymptomatic and presymptomatic cases could be a substantial challenge to epidemic control, and the use of traditional NPI measures and policies were necessary to control the COVID-19 outbreak.

**Table 3.2** Rate of Viral Transmissibility in Wuhan Before and After Implementing NPI Measures<sup>32</sup>

Period	Interventions	Estimated $R_0$ (95% CI)
January 1–10, 2020	None—children on school break	3.88 (3.77–3.99)
January 11–22 ( <i>Chunyun</i> , Chinese New Year)	None—massive population movement	3.86 (3.74–3.97)
January 23–February 1	Drastic social distancing measures with no travel in and out of Hubei <i>cordon sanitaire</i>	1.26 (1.21–1.31)
February 2–18	NPIs with aggressive testing and isolation of positive cases, contact tracing, and quarantine Stay at home orders	0.32 (0.27–0.38)

People who were residing in other countries in the regions such as Hong Kong and Taiwan had experienced and learned lessons from the SARS outbreak and moved quickly to test and quarantine suspected cases, trace potential cases, ban large gatherings, impose social distancing, and enforce universal masking measures and instruct people to stay 1.5 m apart.<sup>33, 34</sup> They prepared hospitals and staff and communicated accurate up-to-date information to the public. As COVID-19 moved westwards with Europe becoming the next epicenter, countries implemented NPI measures. The NPI measures, for 11 countries, were introduced successively from March 2 to March 20 and had a substantial effect on reducing transmission (81% reduction in attack rate) and brought  $R_0$  below 1 (probability  $R_t < 1$  is 99.9%).<sup>35</sup>

The blanket measures to contain a pandemic can come at very high social and economic costs, but they may be necessary to break the chain of disease transmission. In the case of COVID-19, it was necessary to mitigate the worst effects of the disease such as the overwhelming surge in demand for hospital care, particularly intensive care, and the high levels of mortality.

### 3.7 Risk Factors

COVID-19 can affect people of all ages and backgrounds, but the data suggest that some people are more likely than others to get sick if they are exposed to the virus. From the outset of the epidemic, the data from China showed more severe illness and higher rates of infection in older groups and those with preexisting comorbid conditions.<sup>36</sup> Age is an independent risk factor for older people that had no underlying conditions and also being at increased risk of severe illness. For example, people in their 60s are at higher risk for severe illness than people in their 50s, and those in their 50s are at higher risk than those in their 40s. The greatest risk for severe illness is among those aged 80 years or older. Children under 10 are not at risk and less likely to spread the disease. However, children between ages 10 and 19 are at less risk of severe illness but just as likely as adults to spread the disease.<sup>37</sup>

The *Lancet Global Health* recently estimated that one in five individuals worldwide are at increased risk of severe disease, should they become infected, due to an underlying comorbidity and that risk varies considerably with age.<sup>38</sup> The prevalence of one or more comorbidities is approximately 10% by 25 years, 33% by 50 years, and 66% by 70 years. The case fatality rate among those with preexisting comorbid conditions was 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory diseases, 6.0% for hypertension, and 5.6% for cancer. Males were also at twice the risk compared with females. Obesity, classified as a body mass index (BMI) of 30 or above, and severe obesity of BMI of 40, is emerging as an important risk factor in the United States where the prevalence is 40% compared with 24% in Spain, 20% in Italy, and 6.2% in China.<sup>39</sup> Obese people with COVID-19 are more likely to experience severe pneumonia and require ventilation.<sup>40, 41</sup>

People who are in an immunocompromised state because of organ transplants or chemotherapy for cancers are also vulnerable to COVID-19. One study that

considered COVID-19 in immunocompromised patients reported high case of fatality rate which was estimated to be 21.4%.<sup>42</sup> Such a situation presents a conundrum for doctors who need to balance the risk of delaying chemotherapy against the increased risk of infection during the pandemic.

It has been speculated that diseases such as HIV and tuberculosis (TB), which lead to immunocompromised states, are also a risk factor for COVID-19 infection, but at this time there is not enough evidence for a definitive association. In China, TB was the most common comorbidity in COVID-19 patients with 36% concurrently having a TB infection, compared to a general prevalence of 25% in the general population.<sup>43</sup> Furthermore, patients with TB who contracted COVID-19 progressed to severe symptoms much more quickly than those without TB with the time from symptom onset to severe pneumonia averaging 3 days, compared to 7–8 days in cases without TB. For people living with HIV, the risk associated with COVID-19 is inconclusive, and most likely obscured by treatment with antiretrovirals.<sup>37</sup> In Barcelona, 1% of COVID-19 patients who required hospitalization were HIV positive, which is much higher than the HIV prevalence of 0.3% in the population.<sup>44</sup>

Smoking is associated with a high risk of severe symptoms for COVID-19, and a study published by the International Society for the Prevention of Tobacco Induced Diseases found that smokers infected with COVID-19 were 1.4 times more likely to experience severe symptoms and 2.4 times more likely to be admitted to the ICU, require intubation, or die compared to COVID-19 patients who were nonsmokers.<sup>45</sup>

Other groups who need extra precaution are people in closed settings such as prisons, homeless shelters, homes for people with disabilities and developmental or behavioral disorders, refugee camps, food processing plants, and other manufacturing settings.

### 3.8 Conclusion

In summary

- SARS-CoV-2 is highly transmissible and can be identified in droplets, aerosols, and on surfaces before the onset of symptoms. A person can be infectious for up to 14 days or longer.
- Transmission from presymptomatic and asymptomatic cases makes it difficult to contain the spread of disease, and it is therefore recommended that individuals observe good hand hygiene, wear masks, and keep a physical distance of 1.5 m (6 ft) from others.
- The risk of transmission varies by settings, but a closed environment with poor ventilation, large crowds, and prolonged contact with an infected person increase the likelihood of secondary infection.
- Child-to-adult transmission appears uncommon and children do not seem to be at risk for COVID-19 unless there are comorbidities.

- Increasing age and underlying comorbidities increase the risk of severe illness and mortality.
- In the absence of a vaccine or effective treatment, the immune response should be strengthened through a healthy diet, regular exercise, and at least 8 hours of sleep.

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# Outpatient Management: Mild and Moderate Symptoms of COVID-19



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## List of Abbreviations

ACAAI	American College of Allergy, Asthma and Immunology
ACE II	Angiotensin-converting enzyme II
ATII	Angiotensin II
ROS	Reactive oxygen species
WHO	World Health Organization

### 4.1 Introduction

Symptoms of COVID-19 can range from an asymptomatic course to a myriad of manifestations. Most people will experience mild-to-moderate respiratory illness symptoms. The World Health Organization (WHO) reports that “80% of infections are mild or asymptomatic; 15% of infections are severe, which require oxygen; and 5% of infections are critical, requiring ventilation.” For patients with a mild clinical course, the most common symptoms are flu-like (ie, fever, dry cough, shortness of breath/difficulty breathing, fatigue, sore throat, chills, and muscle pain). A subset of patients with initially mild symptoms may experience a rapid worsening of their condition, requiring hospitalization. This chapter discusses the current management strategies for mild-to-moderate disease that doesn’t require hospitalization and can be handled at home.

### 4.2 COVID-19 Overview of Symptoms

The virus has an incubation period of 2–14 days; on average, patients report symptoms within 3–5 days.<sup>1</sup> The time from infection to symptom manifestation appears to be based on the immune system functioning of the individual. Older adults, aged

>70 years, having shorter incubation periods and more severe disease courses. Those under 18 years of age are less likely to present with the hallmark symptoms of fever and cough compared to adults aged 18–64.<sup>2</sup>

CDC reports that 83–99% of COVID patients experience fever, 59–82% cough, 44–70% fatigue, 40–84% anorexia, 31–40% shortness of breath, 28–33% sputum production, and 11–35% myalgia.<sup>3</sup> A study of 1099 patients across 552 hospitals in China found that over 75% of cases reported a fever ranging between 37.5°C and 39.0°C (99.5°F–102.2°F), 68.7% reported a cough, 38.1% fatigue, and 33.7% sputum production.<sup>4</sup> The same study found that comorbidities such as hypertension and diabetes could influence the severity of disease progression. Table 4.1 also provides information for the findings of other coexisting disorders.

### 4.3 Current Management Strategies for Mild Disease

It is currently recommended that those with mild symptoms (or previous exposure to the virus) stay home. For most patients, the disease is self-limited and does not require medical care. To manage symptoms, the Centers for Disease Control and Prevention recommends rest, staying hydrated, and the use of over-the-counter medicines like acetaminophen.<sup>5</sup>

Infected persons living in a household with others should take extra precautions to avoid the spread of the virus. The most important prophylaxis is frequent handwashing or the use of an alcohol-based hand sanitizer if handwashing is not possible. It is also recommended for all individuals to not touch their face, especially their nose, eyes, and mouth; this precautionary step decreases the risk of viral entry into the body. To protect others living in the household from becoming infected, CDC recommends a frequent sanitization of shared surfaces, isolation and social distancing of the infected person from the rest of the household (including pets), and the infected person wearing a mask when around others. If possible, the infected person should even have his or her own separate bathroom for the duration of illness. Patients who use CPAP (continuous positive airway pressure) or BiPAP (bilevel positive airway pressure) machines and nebulized medications should not use them when other people are around as it can become aerosolized.

The WHO updated the criteria for discharge from isolation as part of the clinical care pathway of a COVID-19 patient. These criteria apply to all COVID-19 cases regardless of isolation location or disease severity. The criteria for discharging patients from isolation (i.e., discontinuing transmission-based precautions) without requiring retesting:

- For symptomatic patients: 10 days after symptom onset, plus at least three additional days without symptoms (including without fever and without respiratory symptoms) and
- For asymptomatic cases: 10 days after positive test for SARS-CoV-2.

**Table 4.1** Clinical Characteristics of the Study Patients, According to Severity and the Presence or Absence of the Primary Composite End Point<sup>a</sup>

Characteristics	All Patients (N = 1099)	Disease Severity		Presence of Primary Composite End Point <sup>b</sup>	
		Nonsevere (N = 926)	Severe N = 173	Yes (N = 67)	No (N = 1032)
Age					
Median (IQR)—years	47.0 (35.0–58.0)	45.0 (34.0–57.0)	52.0 (40.0–65.0)	63.0 (53.0–71.0)	46.0 (35.0–57)
Distribution—no./total no. (%)					
0–14 years	9/1011 (0.9)	8/848 (0.9)	1/163 (0.6)	0	9/946 (1.0)
15–49 years	557/1011 (55.1)	490/848 (57.8)	67/163 (41.1)	12/65 (18.5)	545/946 (57.6)
50–64 years	292/1011 (28.9)	241/848 (28.4)	51/163 (31.3)	21/65 (32.3)	271/946 (28.6)
>65 years	153/1011 (15.1)	109/848 (12.9)	44/163 (27.0)	32/65 (49.2)	121/946 (12.8)
Female sex—no./total no. (%)	459/1096 (42.9)	386/923 (41.8)	73/173 (42.2)	22/67 (32.8)	437/1029 (42.5)
Smoking history—no./total no. (%)					
Never smoked	927/1085 (85.4)	793/913 (86.9)	134/172 (77.09)	44/66 (66.7)	883/1019 (86.7)
Former smoker	21/1085 (1.9)	12/913 (1.3)	9/172 (5.2)	5/66 (7.6)	16/1019 (1.6)
Current smoker	137/1085 (12.6)	108/913 (11.8)	29/172 (16.9)	17/66 (25.8)	120/1019 (11.8)
Exposure to source of transmission within past 14 days—no./total no. (%)					
Living in Wuhan	483/1099 (43.9)	400/926 (43.2)	83/173 (48.0)	39/67 (38.2)	444/1032 (43.0)
Contact with wildlife	13/687 (1.9)	10/559 (1.8)	3/128 (2.3)	1/41 (2.4)	12/646 (1.9)
Recently visited Wuhan <sup>c</sup>	193/616 (32.3)	366/526 (31.6)	27/90 (30.0)	10/28 (35.7)	183/388 (31.1)

(continued)

Table 4.1 (continued)

Characteristics	All Patients (N = 1099)	Disease Severity	Presence of Primary Composite End Point <sup>b</sup>
Had contact with Wuhan residents <sup>c</sup>	442/611 (72.3)	376/522 (72.0)	19/28 (67.9)
Median incubation period (IQR)—days <sup>d</sup>	4.0 (2.0–7.0)	4.0 (2.8–7.0)	4.0 (1.0–7.5)
Fever on admission			
Patients—no./total no. (%)	473/1081 (43.8)	391/910 (43.0)	24/66 (36.4)
Median temperature (IQR)—°C	37.3 (36.7–38.0)	37.3 (36.7–38.0)	36.8 (36.3–37.8)
Distribution of temperature—no./total no. (%)			
<37.5°C	608/1081 (56.2)	519/910 (57.0)	42/66 (63.6)
37.05–38.0°C	238/1081 (22.0)	201/910 (22.1)	10/66 (15.2)
38.1–39.0°C	197/1081 (28.2)	160/910 (17.6)	11/66 (16.7)
>39.0°C	38/1081 (3.5)	30/910 (3.3)	3/66 (4.5)
Fever during hospitalization			
Patients—no./total no. (%)	975/1099 (88.7)	816/926 (88.1)	59/67 (88.1)
Median highest temperature (IQR)—°C	38.3 (37.8–38.9)	38.3 (37.8–38.9)	38.5 (38.0–39.0)
<37.5°C	92/926 (10.9)	79/774 (10.2)	3/54 (5.6)
37.05–38.0°C	286/926 (30.9)	251/774 (32.4)	20/54 (37.0)
38.1–39.0°C	434/926 (46.9)	356/774 (46.0)	21/54 (38.9)
>39.0°C	114/926 (12.3)	88/774 (11.4)	10/54 (18.5)
			916/1032 (88.8)
			38.3 (37.8–38.9)
			89/872 (10.2)
			266/872 (30.5)
			413/872 (47.4)
			104/872 (11.9)

Symptoms—no. (%)						
Conjunctival congestion	9 (0.8)	5 (0.5)	4 (2.3)	0	9 (0.9)	
Nasal congestion	53 (4.8)	47 (5.1)	6 (3.5)	2 (3.0)	51 (4.9)	
Headache	150 (13.6)	124 (13.4)	26 (15.0)	8 (11.9)	142 (13.8)	
Cough	745 (67.8)	623 (67.3)	122 (70.5)	46 (68.7)	699 (67.7)	
Sore throat	153 (13.9)	130 (14.0)	23 (13.3)	6 (9.0)	147 (14.2)	
Sputum production	370 (33.7)	309 (33.4)	61 (35.3)	20 (29.9)	350 (33.9)	
Fatigue	419 (38.1)	350 (37.8)	69 (39.9)	22 (32.8)	397 (38.5)	
Hemoptysis	10 (0.9)	6 (0.6)	4 (2.3)	2 (3.0)	8 (0.8)	
Shortness of breath	205 (18.7)	140 (15.1)	65 (37.6)	36 (53.7)	169 (16.4)	
Nausea or vomiting	55 (5.0)	43 (4.6)	12 (6.9)	3 (4.5)	52 (5.0)	
Diarrhea	42 (3.8)	32 (3.5)	10 (5.8)	4 (6.0)	38 (3.7)	
Myalgia or arthralgia	164 (14.9)	134 (14.5)	30 (17.3)	6 (9.0)	158 (15.3)	
Chills	126 (11.5)	100 (10.8)	26 (15.0)	8 (11.9)	118 (11.4)	
Signs of infection—no (%)						
Throat congestion	19 (1.7)	17 (1.8)	2 (1.2)	0	19 (1.8)	
Tonsil swelling	23 (2.1)	17 (1.8)	6 (3.5)	1 (1.5)	22 (2.1)	
Enlargement of lymph nodes	2 (0.2)	1 (0.1)	1 (0.6)	1 (1.5)	1 (0.1)	
Rash	2 (0.2)	0	2 (1.2)	0	2 (0.2)	

(continued)

Table 4.1 (continued)

Characteristics	All Patients (N = 1099)	Disease Severity	Presence of Primary Composite End Point <sup>b</sup>
Coexisting disorders			
Any	261 (23.7)	194 (21.0)	39 (58.2)
Chronic obstructive pulmonary disease	12 (1.1)	6 (0.6)	7 (10.4)
Diabetes	81 (7.4)	53 (5.7)	18 (26.9)
Hypertension	165 (15.0)	124 (23.4)	24 (35.8)
Coronary heart disease	27 (2.5)	17 (1.8)	6 (9.0)
Cerebrovascular disease	15 (1.4)	11 (1.2)	4 (6.0)
Hepatitis B infection <sup>c</sup>	23 (2.1)	22 (2.4)	1 (1.5)
Cancer <sup>f</sup>	10 (0.9)	7 (0.8)	1 (1.5)
Chronic renal disease	8 (0.7)	5 (0.5)	2 (3.0)
Immunodeficiency	2 (0.2)	2 (0.2)	0

<sup>a</sup>The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. COVID-19 denotes coronavirus disease 2019, and IQR interquartile range.

<sup>b</sup>The primary composite end point was admission to an intensive care unit, the use of mechanical ventilation, or death.

<sup>c</sup>These patients were not residents of Wuhan.

<sup>d</sup>Date regarding the incubation period were missing for 808 patients (73.5%).

<sup>e</sup>The presence of hepatitis B infection was defined as a positive result testing for hepatitis B surface antigen with or without elevated levels of alanine or aspartate aminotransferase.

<sup>f</sup>Included in this category is any type of cancer.

### 4.3.1 Management of Underlying Conditions with COVID-19 Infection

In general, patients with comorbidities are not more likely to get infected with COVID-19 compared to the general population. People with the underlying chronic conditions such as diabetes, obesity, HIV, other immunocompromised states, and hypertension are more likely to suffer from complications when infected with the virus. For patients with comorbidities, recommendations may vary and will be provided by the health-care practitioner, but general guidance is as follows:

- *Respiratory disease:* Patients with asthma are advised to follow the general precautions listed above as well as to continue the established asthma action plan. The American College of Allergy, Asthma and Immunology (ACAAI) issued a statement to encourage adherence to allergy and asthma maintenance regimens. According to the ACAAI, there is no evidence that intranasal or inhaled corticosteroids increase the risk of getting the COVID-19 infection or lead to a worse outcome if someone does get infected.<sup>6</sup>
- *Cardiovascular conditions:* Older patients with cardiovascular comorbidities may have an added protection against severe disease from the virus if on angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) according to an observational study conducted by United Health Group and the Yale University School of Medicine.<sup>7</sup> A meta-analysis also found that ACE inhibitors/ARBs do not increase the risk of infection nor developing severe disease.<sup>8</sup>
- *Diabetes:* Patients who have diabetes must maintain blood glucose level as infection with COVID-19 can lead to increased complications; this is because high blood glucose levels can suppress the immune system. These complications can come in the form of kidney failure and diabetic ketoacidosis, which are both life-threatening and require immediate medical attention.<sup>4</sup> Diabetic patients must continue to take prescribed medications in addition to avoiding the risk factors for the development of COVID-19.
- *Immunocompromised:* People that are immunocompromised are at an increased risk of developing infections because the immune system is the body's defense against pathogens. Immunocompromised individuals include but are not limited to, patients with cancer, transplants, and HIV. These patients should continue with their normal treatment regimen for their underlying disease even if it involves immunosuppressants. If a patient develops a fever of 100.4°F (38°C) or higher, he/she must call their physician immediately.<sup>9</sup>
- *Obesity:* An often underestimated comorbidity that many Americans face is obesity. It is reported that 42% of adults are obese and 9% are severely obese.<sup>10</sup> Obesity is associated with decreased expiratory reserve volume, functional capacity, and respiratory system compliance. It is also associated with increased inflammatory cytokines, which may contribute to the increased morbidity associated with obesity in COVID-19 infections.<sup>5</sup> For these reasons, patients suffering from obesity should work with their health-care practitioner to develop a lifestyle plan that includes diet modification and frequent exercise.<sup>11</sup>



### 4.3.2 Protective Health Measures

Quality sleep (preferably of 7–8 h in duration), exercise, and a well-balanced diet rich in fruits and vegetables help to bolster the innate immune system. The innate immune system is our body's first line of defense against a variety of pathogens before our adaptive immune system can offer additional and stronger protection. It takes about 4–7 days for the adaptive immune response to set in; therefore, in the initial stages of infection, the innate immune response is essential for fighting and clearing the virus (see Chapter 2).

Vitamins and supplements, such as zinc and Vitamin C, while not officially recognized as treatments for mild symptoms, can possibly be cheap, low-risk, and efficacious prophylaxis because of their immune-modulating effects on the immune system. Studies have shown that zinc can inhibit the replication of some viruses such as the original coronavirus and arterivirus, thus decreasing the severity of disease.<sup>1</sup> Part of how COVID-19 causes disease is by blocking the angiotensin converting-enzyme II (ACE II) receptor, resulting in increased levels of angiotensin II (ATII) and decreased levels of angiotensin 1, 7 (AT 1,7). Both of these changes lead to the formation of reactive oxygen species (ROS) like superoxides, which cause endothelial cell dysfunction; this state predisposes the patient to thrombosis in organs like lungs, and as a result impairing oxygen delivery.<sup>12</sup> Vitamin C is a well-known antioxidant and can potentially protect against the effect of ROS, thus decreasing the severity of disease and the chance of developing serious complications from the virus. A 2017 study found that daily or weekly vitamin D supplementation was protective against acute respiratory tract infection,<sup>5</sup> which can make this a helpful prophylaxis against COVID-19.

Home oxygen therapy can be considered effective in patients with mild hypoxia with improvement in saturation with oxygen by nasal cannula who can reliably adhere with therapy and follow-up. Such patients will require daily televisits. Thromboprophylaxis at home can be considered in patients at high risk for thrombosis.

Fructose consumption, obesity, and sedentary lifestyle all contribute to chronic systemic inflammation, which results in poor immune function and can render a person more susceptible to developing disease and/or slow recovery/complications from the disease.<sup>13</sup>

## 4.4 Management by Telemedicine

Telemedicine is a method that allows health-care practitioners to provide care to patients through electronic means. It is preferable in most of the outpatient management of COVID-19 patients as it can prevent avoidable in-person medical visits to medical offices/urgent care centers or emergency rooms (ERs), providing relief to a strained health-care system and preventing unnecessary use of personal protective equipment (PPE). For the general public, the advantage of this service is that patients

have an increased access to care in an environment that is most convenient and comfortable to them. In the long term, this can promote adherence to treatment plans and decrease loss-to-follow-up rates. For those that lack adequate health insurance, telemedicine is not only cheaper compared to in-person office visits, but can even be free in some cases.

In his Washington Post article, primary care physician Michael Barnett writes, “Much of the actual work of primary care happens when patients aren’t in the office, whether doctors are coordinating with three specialists to tweak a complex medication regimen or finding a hospice agency for an ailing patient. The only reason we deliver almost all primary care through office visits is because that is what insurers will pay for”.<sup>14</sup> For COVID-19 patients with mild symptoms that do not require hospitalization, telemedicine is a great option to provide care while reducing the risk of transmission to the vulnerable public who rely on in-person clinic visits. Patients who are considered stable enough to be managed at home are risk-stratified into low, moderate, and high risk to determine the frequency of follow-up visits.

A large part of telemedicine is a conversation between the health-care provider and the patient. Most health-care practitioners prefer to conduct telemedicine services, such as physical examinations, physical therapy, and mental health services, through video chat or telephone conversation. This allows the health-care practitioner to observe the general appearance of the patient and their ability to perform tasks the provider guides them. Providers can take patient vitals by calculating respiratory rate based on observation and providing equipment for patients to monitor their own health such as electronic blood pressure machines and blood glucose monitors. During video televisits, clinicians can judge the level of dyspnea, oxygen saturation, and mental status by observation and can inquire about other symptoms such as orthostasis, dizziness, falls, changes in sensation of smell and taste, hypotension, and urine output. Based on the examination, the provider can then recommend tests or treatments that can be delivered to a patient from a pharmacy near them or if in-person evaluation is necessary. In a *New York Times* article, Dr. Emil Baccash, a geriatrician in Brooklyn, N.Y. said of telemedicine, “Telemedicine is not a substitute for seeing and physically examining a patient. But there are some patients, especially elderly patients, who can’t get out of the house. I can talk to them and look at their problem on my computer, take a snapshot, say, of a leg infection and enter it directly into their medical record. If a blood test is needed, I can have a lab technician come to their house”.<sup>15</sup> Patients who are less reliable to self-monitor and report may need more intense follow-up to continue the management at home.

Telemedicine also offers a health-care practitioner the opportunity to observe a patient’s living environment. Environment can exacerbate certain conditions or predispose certain demographics, like the elderly, to injury. Rural communities can also benefit from telemedicine as many members of this community have trouble with accessing care due to the deficit of health-care centers and the distance to these sites.

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# Pulmonary Manifestations of COVID-19



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## List of Abbreviations

ARDS	Acute respiratory distress syndrome
BTS	British Thoracic Society
COPD	Chronic obstructive pulmonary disease
HFNC	High flow nasal cannula
ICU	Intensive care unit
ICS	inhaled corticosteroid
ISTH	International Society on Thrombosis and Haemostasis
NICE	National Institute of Clinical Excellence
PE	Pulmonary embolism
PEEP	Positive end expiratory pressure
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SRF	Severe respiratory failure
VTE	Vascular thromboembolism

## 5.1 Introduction

The effect of COVID-19 on the respiratory system has become very well recognized since this novel coronavirus has been established. The rapid spread of COVID-19 along with its burden on the respiratory system has pressured health-care systems into managing the health status of patients. It is important to comprehensively understand how COVID-19 manifests in order to overcome this pandemic in a globally resource-limited climate. This chapter summarizes the pathophysiology, symptoms, and associations with other respiratory diagnoses, as well as clinical management.

## 5.2 Origins, Transmission, and Pathogenesis of COVID-19 Disease

In December 2019, there was an outbreak of an unknown virus at a seafood market in Wuhan, China; initially, it was referred to as pneumonia of unknown origin. It was thought that the transmission was zoonotic and only the people working in the seafood market were affected. However, human-to-human transmission was later established.<sup>1</sup> World Health Organization (WHO) declared a public health emergency of international concern on January 30, 2020, and pandemic on March 30, 2020.<sup>2</sup>

The novel coronavirus was named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) following on from SARS-CoV, which caused acute respiratory distress syndrome (ARDS) and resulted in high mortality during 2002–2003. Coronaviruses are a family of enveloped, positive, single-stranded RNA viruses that are classified within the Coronavirus family and Nidovirales order.<sup>3</sup>

The predominant mode of transmission is from respiratory droplet spread by coughing, sneezing, and talking, which can easily contaminate surfaces and spread the virus within the households.<sup>4</sup> There is an evidence for the spread by a direct contact with infected secretions or large and small aerosol droplets (Figure 5.1). Immunity develops soon after infection, but wanes gradually over time. It is unknown if reinfection is common.

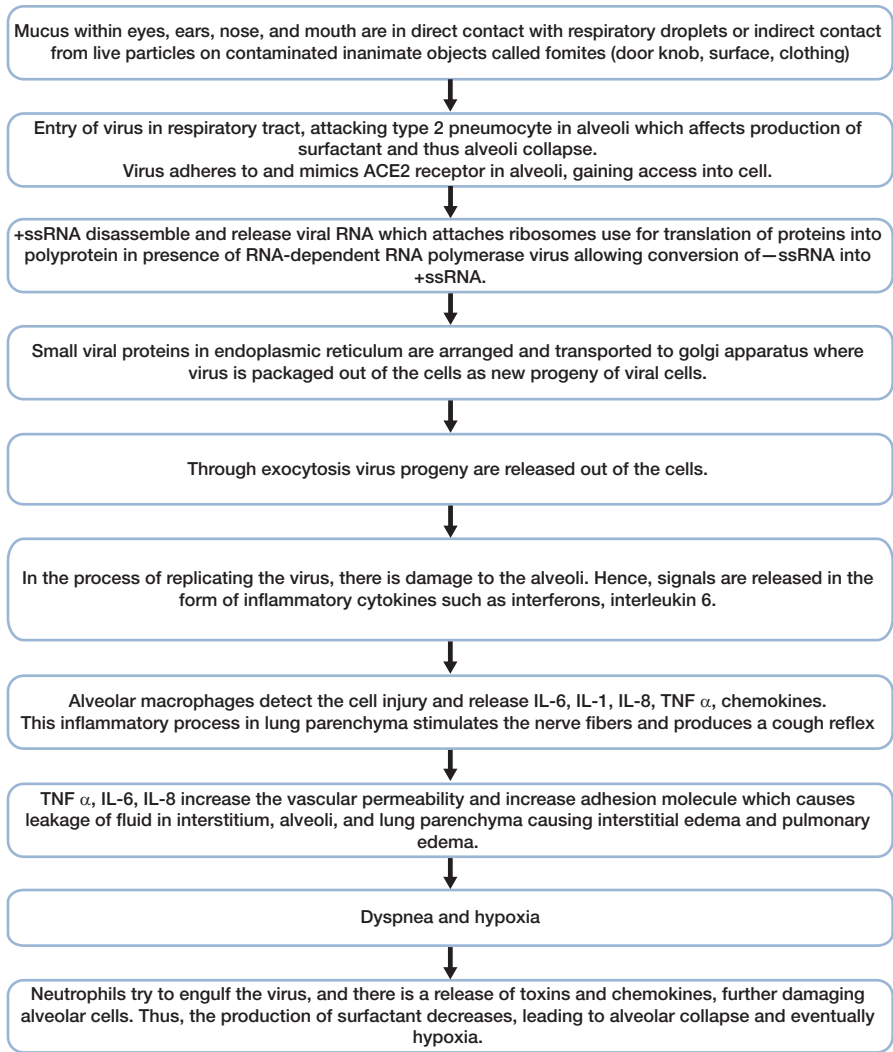
High-risk populations include children, pregnant women, immunocompromised patients, health-care providers, and elderly people. Incubation period can extend up to 14 days from the onset of exposure. Some individuals can be asymptomatic or may have mild severity of fever, shortness of breath, and cough due to a good immune system.

Most COVID-19 patients had mild symptoms in the early onset of disease; however, the condition of some patients declined in the latter half of the disease or during the recovery phase. The mortality of many patients is attributed to the rapid development of ARDS and multiorgan failure as a result of a cytokine storm. An effective suppression of the cytokine storm is a pivotal way to prevent the deterioration of patients with COVID-19 infection and save the patients' lives.

## 5.3 Pathophysiology

The complexity of a cytokine storm's pathogenesis involves the loss of regulatory control of pro-inflammatory cytokine production, both locally and systemically, thereby causing excessive immune responses with potential immune damage to the human body.<sup>5</sup> The cytokine storm is detailed in (Figure 5.2).

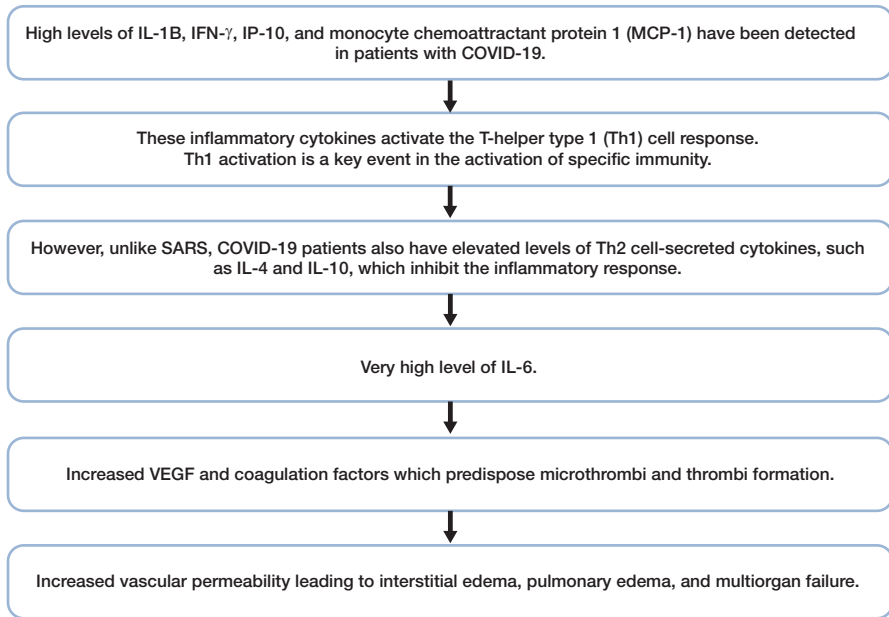
Increased serum levels of IL-2R and IL-6 in patients with COVID-19 are associated with an increased severity of disease. Moreover, other studies have found patients in the intensive care unit (ICU) displaying increased serum levels of granulocyte colony-stimulating factor, IP-10, MCP-1, macrophage inflammatory



**Figure 5.1** Flowchart describing the pathogenesis of COVID-19.

protein-1A, and tumor necrosis factor-alpha (TNF- $\alpha$ ), compared to COVID-19 patients from general wards.<sup>6</sup> Therefore, this suggests that the cytokine storm is positively correlated with disease severity. Given that cytokine storms involve hyperinflammation, immunosuppression is likely to be beneficial.<sup>5</sup>

The corresponding signs and symptoms include fever, cough, shortness of breath, myalgia, fatigue, ARDS, arrhythmia, and shock. Laboratory results demonstrated altered liver function tests, azotemia, elevated troponin T, elevated d-dimer, and elevated IL-6 levels.



**Figure 5.2** Flowchart describing the pathophysiology of a cytokine storm within COVID-19.

### 5.3.1 Symptoms

It is critical to understand how patients will present clinically for safe triage and risk assessment, especially considering signs and symptoms of COVID-19 are nonspecific following an incubation period of 2–14 days.<sup>7</sup> Moreover, presentations can range from patient's being asymptomatic to death.

A comprehensive joint report produced by WHO and China on COVID-19 ( $n = 55,924$ ) demonstrated COVID-19 patients commonly present with pyrexia (87.9%), dry cough (67.7%), sputum production (33.4%), and dyspnea (18.6%). Other common symptoms are myalgia/arthralgia, chills, headache, sore throat, nasal congestion, anosmia, and ageusia.<sup>7–9</sup> Early reports from China also stated that a few patients experienced rhinorrhea and haemoptysis.<sup>10, 11</sup>

Anosmia and ageusia are more commonly found within COVID-19 patients who are younger and not hospital inpatients. The majority of patients with the loss of taste or smell noticed an improvement within 2 weeks.<sup>12</sup>

Similar findings were present among pregnant patients who developed COVID-19 pneumonia.<sup>13, 14</sup> Interestingly, studies have shown that children may be less likely to be symptomatic or develop severe symptoms compared to adults; however, they are just as likely to be infected. Therefore, the risk of transmission from children is yet to be understood.<sup>15, 16</sup>

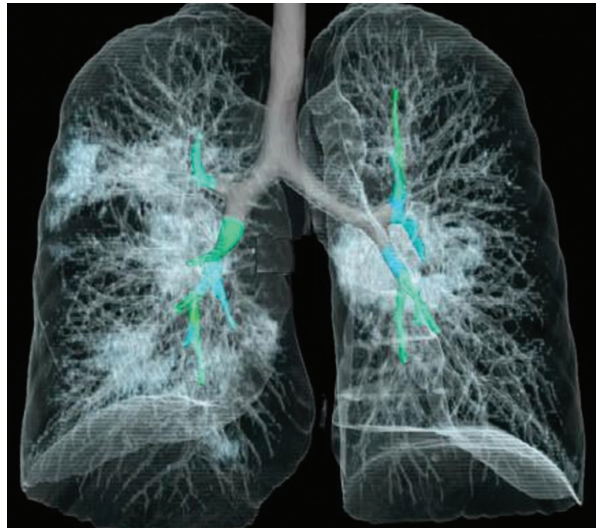
### 5.3.2 Happy Hypoxics

Among the many surprises of the novel coronavirus, some patients seem to defy the basic physiology of hypoxia as they can be well observed generally, and to describe themselves as comfortable with no signs of distress. For such patients, SpO<sub>2</sub> and SaO<sub>2</sub> have been reported as low as 62% and 69%, respectively. Clinicians call them happy hypoxics.<sup>17, 18</sup>

### 5.3.3 Mechanism

Swelling and inflammation in the lungs is likely to make oxygen perfusion difficult (Figure 5.3). There is evidence that COVID-19 can cause blood clotting with the development of microthrombi, thus affecting the entire body. With a focus on the lungs, microthrombi can occlude the very distal vessels participating in gas exchange. Interestingly, reports have shown anticoagulation drastically improving bluish discoloration of toes and shortness of breath.<sup>18</sup> Therefore, the severity of COVID-19 can be indicated by d-dimer levels as it reflects coagulation cascade activation, organ failure, and cytokine storm. A high level of d-dimer during admission is associated with high mortality and morbidity. As such, anticoagulation will definitely be a cornerstone in the management of COVID-19 patients.

**Figure 5.3** Lung CT scan of a COVID-19-positive patient demonstrating a lack of distal perfusion.<sup>19</sup>





## 5.4 Respiratory Failure

SARS-CoV causes acute pneumonia and is associated with a high mortality as relatively clinically stable patients can suddenly deteriorate to severe respiratory failure (SRF). The most characteristic symptom of patients with COVID-19 is respiratory distress, and most of the patients admitted to ICU cannot breathe spontaneously.<sup>20</sup> This is supported by a study which found more than half of the patients admitted with dyspnea needed intensive care—of which 46–65% of the patients worsened in a short period of time and died due to respiratory failure.<sup>20</sup>

The sudden clinical deterioration 7–8 days after the onset of symptoms suggests that SRF in COVID-19 is driven by a unique pattern of immune dysfunction.<sup>21</sup> All patients with SRF displayed either cytokine storm or depletion of CD4 lymphocytes, CD19 lymphocytes, and natural killer (NK) cells. The production of TNF- $\alpha$  and IL-6 by circulating monocytes was observed to be sustained, unlike in bacterial sepsis or influenza. This was partially restored by the IL-6 blocker tocilizumab.

Another study noticed that COVID-19 patients with acute respiratory failure present with severe hypercoagulability.<sup>22</sup> Therefore, the treatment of respiratory failure should include anticoagulation along with an appropriate management of the cytokine storm and ARDS.

## 5.5 COVID-19 and Pulmonary Embolisms

Acute infections have been known to cause a transient increased chance for a concurrent pulmonary embolism (PE) in the absence of other risk factors for vascular thromboembolisms (VTEs).<sup>23</sup> This has been highlighted further in a case report of a COVID-19 patient.<sup>24</sup> Nonetheless, many patients will have a lengthy hospitalized disease course with COVID-19 introducing immobilization as a risk factor for PEs too.

D-dimer levels are typically used as a crude indicator for the chance of a patient having a thrombus formation. However, elevated d-dimer levels may be misinterpreted due to its acute-phase reactant properties in light of the COVID-19 infection without appreciating a coexisting PE.

Considering a PE has a high risk of mortality if it is not managed, it is pivotal for a patient's outcome to identify PEs as soon as possible. However, an autopsy study of a few COVID-19-positive patients revealed that in patients, which were not suspected to have VTE, the direct cause of death was from a PE and others experienced deep vein thrombosis.<sup>25</sup> Although the study had a small sample size, it emphasizes the need to identify and manage the risk of developing VTE, and thereby improving mortality.

More specifically with regard to management, the relationship between PEs and COVID-19 has not been extensively studied; the risk and benefit of prophylactic or therapeutic anticoagulation are to be determined. Currently, the International Society on Thrombosis and Haemostasis (ISTH) encourages investigating patients who require admission into hospital with d-dimer level, prothrombin time, platelet

**Table 5.1** Management of VTE Using LMWH for a Patient Weighing 70 kg and Has a CrCl >30 mL/min<sup>29</sup>

Standard risk patient	Weight adjusted prophylactic dose LMWH, eg, dalteparin 5000 units OD, enoxaparin 40 mg OD
High-risk patient	Intermediate dose LMWH, eg, dalteparin 5000 units BD, enoxaparin 40 mg BD
Proven or suspected acute VTE	Therapeutic dose LMWH (BD dosing may be preferred with critical care patients)

count, and fibrinogen level as markers of prognosis in COVID-19,<sup>26</sup> particularly considering that increased d-dimer levels are associated with an increased mortality of COVID-19 patients.<sup>27</sup> ISTH, supported by experts and physicians across China and Europe,<sup>28</sup> also advises the use of prophylactic low-molecular-weight heparin (LMWH) in all patients requiring admission for COVID-19, in the absence of contraindications, and with monitoring for patients who have severe renal impairment.<sup>26</sup> The use of LMWH would reduce the risk of developing a PE, as well as decrease inflammation caused by COVID-19 and other comorbidities.<sup>26</sup>

The British Thoracic Society (BTS) has suggested possible dosages, using an example of a 70-kg patient with creatinine clearance (CrCl) > 30 mL/min as outlined in Table 5.1. Patients at high risk of developing VTE following discharge can be considered for extended thromboprophylaxis.<sup>29</sup> Nevertheless, BTS encourages liaising with hematologists to formulate local protocols.

Cases published thus far have generally shown patients being managed for coronavirus and receiving prophylactic anticoagulation show an improvement before clinically deteriorating due to hypoxemia and increasing d-dimer levels, as well as require further anticoagulation to manage the PEs.<sup>30,31</sup> This further justifies d-dimer testing throughout an admission, coupled with using computed tomography pulmonary angiogram for patients with high d-dimer levels on admission or sudden clinical decline to quickly diagnose a PE.

## 5.6 COVID-19 and COPD

Chronic obstructive pulmonary disease (COPD) is known to increase the mortality rates among community-acquired pneumonias, whereby patients are admitted to ICUs more frequently.<sup>32</sup> As COVID-19 can be rapidly transmitted within a population, it is important to prepare for COVID-19 presentations with a background of COPD. Especially since COPD patients may be more susceptible to COVID-19, a study has shown that patients with a history of COPD express increased levels of ACE2 receptors, the reported entry gate of the virus.<sup>33,34</sup> Meta-analysis showed over fivefold increased risk for COPD patients to develop severe COVID-19 infections.<sup>35</sup> The association between COPD and COVID-19 is important to understand to risk-stratify patients and optimize the allocation of resources.

Guidelines set by the National Institute of Clinical Excellence (NICE) in the UK advise patients with an existing COPD management plan, which involves inhaled corticosteroids (ICS), to continue adherence and for professionals to delay any plans to withdraw it.<sup>36</sup> With regard to self-management, NICE advises patients to follow their tailored rescue pack if they believe they are experiencing an exacerbation, as opposed to patients who believe they are experiencing COVID-19 symptoms who should not start oral corticosteroids and/or antibiotics.<sup>36</sup> This poses a problem since management is dependent upon patients to identify the differences between typical exacerbation symptoms and those caused by COVID-19, especially for patients who have been diagnosed with COPD recently.

Contradictory meta-analysis studies have been published regarding the effect of smoking and COPD upon COVID-19 outcomes. Lippi et al.<sup>37</sup> did not find an association between active smoking and COVID-19 in a sample study of 1399 patients. However, Zhao et al.<sup>38</sup> demonstrated a twofold increase in developing severe COVID-19 for active smokers, which is also supported by Alqahtani et al.<sup>39</sup> Despite conflicting evidence, smoking cessation continues to be strongly encouraged for the management of COPD and COVID-19 by NICE.<sup>36</sup>

## 5.7 COVID-19 and Asthma

Asthma can be triggered generally by viral illness, poor adherence to medication, and allergens. Therefore, it is important to identify if COVID-19 specifically has exacerbated symptoms and if management needs to be tapered differently to usual protocol.

A study found that the prevalence of asthma among COVID-19 patients was higher than the national average.<sup>40</sup> However, once the age, gender, and comorbidities were accounted for in the data, asthma was not found to increase the risk of COVID-19 patients being hospitalized.<sup>40</sup> Similarly, ICS and/or systemic corticosteroids were not found to increase the risk of hospitalization.<sup>40</sup>

Systemic steroid treatment may increase the viral load, thus increasing the burden of symptoms resulting in clinical decline. However, there is some early evidence from sputum suggesting that ICS can reduce ACE2 and TMPRSS2 gene expression.<sup>41</sup> WHO has further conflicting evidence to counter ICS potentially being helpful at early stages.<sup>42</sup> Therefore, the use of ICS needs to be studied comprehensively to understand its effect upon the susceptibility and severity of COVID-19.

Furthermore, the use of nebulizers is generally effective in managing asthmatic patients; however, it is an aerosol-generating treatment, which is best avoided within health-care environments. Instead, for such circumstances, it is recommended to use inhalers containing dry powder or metered dose inhalers accompanied by a valve-holding chamber.<sup>43</sup>

Biologic treatment is an interesting topic for the management of asthma. Sound evidence supports moderate to severe patients with clinical indications to have

therapies targeting IL-5, IL-4/IL-13, and IGE.<sup>44</sup> The lack of evidence to suggest biologic treatment is possibly harmful, in the context of COVID-19, which implies it can be used with caution if the drug is effective and well tolerated.<sup>45</sup>

The main deterrent for a poor outcome with COVID-19 appears to be well-managed asthma, as well as adherence to general advice such as hand hygiene, shielding in certain groups of asthmatics, social distancing, effective inhaler technique, and avoiding known triggers.

## 5.8 COVID-19 and Lung Cancer

Oncology societies and national authorities have been quick to issue guidelines on cancer care during the pandemic offering guidance and training to manage patients with cancer while this pandemic goes on—especially considering individuals who are immunocompromised and over 60 years are at high risk of becoming infected with COVID-19.<sup>46</sup> As a result, the UK, together with several other countries, has generally suspended elective procedures.

NHS England warned that certain groups are particularly vulnerable to serious illness if they become infected with SARS-CoV-2. These groups include individuals who are undergoing active chemotherapy or radical radiotherapy for lung cancer, and patients with cancers of the blood or bone marrow.<sup>47</sup> This is supported by a study done in China observing that non-small-cell cancer patients had higher incidence of COVID-19 especially when the age is more than 60 years. Patients with lung cancer have more severe COVID-19 than those without lung cancer.<sup>48</sup> This has been further highlighted in Italy whereby 20% of COVID-19 deaths had a concurrent active cancer.

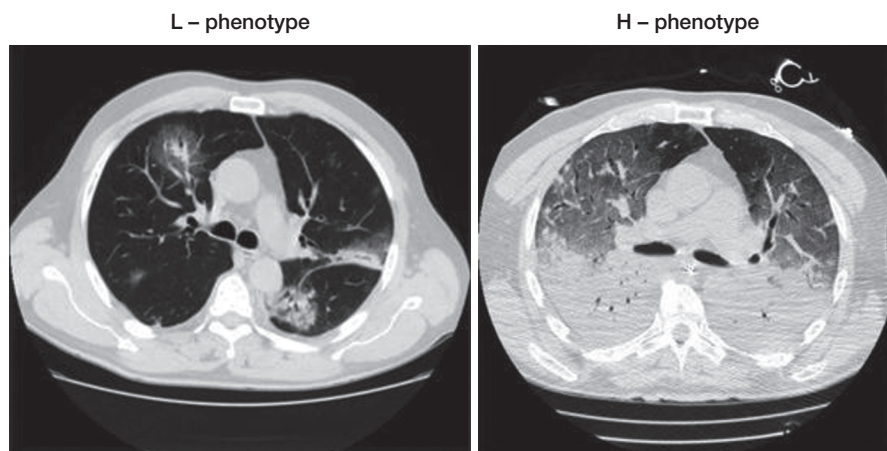
## 5.9 Acute Respiratory Distress Syndrome

ARDS is the most common complication of severe COVID-19. It is a clinical syndrome characterized by severe respiratory distress, hypoxemia, and noncardiogenic pulmonary edema.

### 5.9.1 Diagnostic Criteria

All four of the following criteria must be present:

1. Acute onset of illness
2. Chest X-ray showing bilateral infiltrates
3. Pulmonary capillary wedge pressure <18 mm Hg or a lack of congestive cardiac failure
4. Refractory hypoxemia with  $p_{aO_2}:F_{iO_2} < 200$ .<sup>49</sup>



**Figure 5.4** Chest CT scans demonstrating the difference between L-type and H-type ARDS.<sup>51</sup>

## 5.9.2 Clinical Features

Symptoms: Fever, shortness of breath, inability to complete sentences, persistent nonproductive cough.

Signs: Tachypnea, tachycardia, low mean BP, hypoxia resistant to oxygen, rhonchi, and egophony throughout lung fields.

## 5.9.3 Types of ARDS

L phenotype of ARDS typically has low elastance, ventilation/perfusion mismatch, low lung weight, and low recruitability (Figure 5.4).<sup>50</sup>

H phenotype of ARDS typically has high elastance, high right-to-left shunt, high lung weight, and high recruitability.<sup>50</sup>

Radiologically chest X-rays show bilateral diffuse pulmonary infiltrates, and CT scans show a bilateral ground glass appearance with consolidation compatible with viral pneumonia. Although severe COVID-19 follows all the criteria of ARDS, mortality was increasing when high positive end expiratory pressure (PEEP) was given to all patients with SARS-CoV-2. In an independent study, atypical presentation of ARDS in COVID-19 patients was observed, thus stressing the importance to modify the management for ARDS to decrease mortality.<sup>52</sup>

A patient may also undergo a transition from L to H phenotype as the disease advances to more severe form. This transition may be determined by inspiratory pleural pressure and esophageal pressure swings. Considering esophageal pressure swings between 5 and 10 cmH<sub>2</sub>0 is generally well tolerated, a swing above 15 cmH<sub>2</sub>0 is indicative of a risk for lung injury and warranting intubation as soon as possible.<sup>53</sup>

## 5.10 Outcome with Ventilated Patients

Patients who are severely compromised will require ventilatory support. Although oxygen delivery may be increased with a non-rebreathe mask or by pronating the patient, additional, albeit limited, measures with non-invasive or invasive ventilation will need to be utilized.<sup>54</sup> Multiple facets of challenges regarding ventilators are becoming more evident with the demand carried by this pandemic. For example, the use of ventilators requires training, maintenance, spare parts, and of course the equipment itself.

Hypoxemia is relatively well tolerated in patients without developing exhaustion or acute respiratory distress;<sup>18</sup> therefore, the optimal time to ventilate patients is difficult to determine. Nonetheless, “happy hypoxic” patients only represent a proportion of COVID-19 cases.

High-flow nasal cannula (HFNC) as a means to support COVID-19 patients has been uncertain and appears to be generally avoided. HFNC has the ability to disperse aerosol, but with the addition of wearing a surgical mask over the nasal cannula, the distance of dispersion is markedly reduced.<sup>55</sup> Since surgical masks cannot be used over oxygen masks, the microbiological contamination of the surroundings is not increased for patients using a surgical mask over HFNC, compared to those supported by oxygen masks.<sup>55</sup> This may be a possible method to manage hypoxemic COVID-19 patients, avoiding intubation.

The use of noninvasive ventilation (NIV) is debatable since it is aerosol generating, thus increasing the risk of further spreading COVID-19 among health-care professionals. This has been countered by, first, ensuring that there is a good interface fitting and the use of PPE by staff will minimize the risk of transmission;<sup>56</sup> second, aerosol generation, and thus risk to staff, was found to be higher with intubation.<sup>57</sup> Therefore, using NIV allows for invasive measures to be reserved for more poorly patients.

Invasive ventilation demonstrated significantly poor outcomes. In the UK, 67% of patients with COVID-19 receiving mechanical ventilation died, as opposed to 22% with viral pneumonias in 3 years prior.<sup>58</sup> Early studies from Wuhan highlighted that mortality rates increased from 52–62% for ICU patients to 86–97% when patients received mechanical invasive ventilation.<sup>59</sup> This is partly explained by 40% of ventilated patients having ARDS, which is associated with high mortality rates in itself.<sup>60</sup> Nonetheless, patients with ARDS and  $\text{paO}_2:\text{FiO}_2 < 150$  had a better survival rate with early intubation, as opposed to using NIV.

The majority of COVID-19 cases, however, are not associated with ARDS; as such, their lungs have near-normal function, which is not likely to be improved with high PEEP.<sup>61</sup> Therefore, other options should be considered.

## 5.11 Treatment

High virus titer and the subsequent strong inflammatory cytokine and chemokine responses are related to the high morbidity and mortality. Generally, prophylactic dose of LMWH is recommended for hospitalized patients with COVID-19 to prevent VTE.<sup>62</sup> Potential treatment with other medication has been discussed below.

### 5.11.1 Interferon (IFN- $\lambda$ )

IFN- $\lambda$  primarily activates epithelial cells and reduces the mononuclear macrophage-mediated pro-inflammatory activity of INF $\alpha\beta$ .<sup>63</sup> Early administration of interferons has certain benefits in reducing viral load and improves the clinical symptoms of patients to a certain extent. However, it fails to reduce mortality rate.

### 5.11.2 Steroids

The timing of administration and the dosage of glucocorticoids are very important to the outcome of the severely ill patients. Administration of glucocorticoids too early inhibits the initiation of the body's immune defense mechanism, thereby increasing the viral load and ultimately leading to aggravation of the disease; which has been reported in non-ICU patients.<sup>63</sup> Timely administration of glucocorticoids in the early stage of inflammatory cytokine storm effectively prevents the occurrence of ARDS and protects the functions of the patients' organs. More specifically regarding the dosage, short-term steroids (3–5 days) are appropriate, and the recommended dose is no more than the equivalent of methylprednisolone 1–2 mg/kg/day. Large doses of glucocorticoid may delay the clearance of coronavirus due to immunosuppression.

### 5.11.3 Tocilizumab

Tocilizumab is an IL-6 antagonist that suppresses the function of the immune system.<sup>63</sup> Tocilizumab itself has a therapeutic effect on the infection-induced cytokine storm. Tocilizumab is effective in treating severely ill patients with extensive bilateral lung lesions, who have elevated IL-6 levels. The first dose was 4–8 mg/kg. The recommended dosage was 400 mg with 0.9% saline diluted to 100 ml. The infusion time was more than 1 h. For patients with poor efficacy of the first dose, a repeat dose can be applied after 12 h, with a maximum of two cumulative doses. Tocilizumab reduces patient morbidity and the need for mechanical ventilation but may fail in very advanced disease.<sup>6</sup>

### 5.11.4 Chloroquine

Chloroquine inhibits the production and release of TNF and IL-6, which indicates that chloroquine may suppress the cytokine storm in patients infected with COVID-19. Chloroquine has an immune-modulating activity and antiviral activity. Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.<sup>63</sup> Chloroquine is a cheap and safe drug that has been used for more than 70 years, and therefore, it is potentially clinically

applicable against the COVID-19. There are various dosing regimens available in the literature.

### 5.11.5 Remdesivir

Remdesivir is a nucleotide analogue prodrug that inhibits viral RNA polymerase activity against SARS-CoV-2. It also inhibits virus infection efficiently in a human cell line and recently recognized as a promising antiviral drug.<sup>64</sup> Compassionate use of remdesivir in case of severe COVID-19 patients demonstrated a clinical improvement in 68% of patients. Effectiveness of a shorter duration of therapy, that is, 5 days as opposed to 10 days, is to be investigated since it would allow the treatment of more patients during the pandemic.

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# Cardiovascular Manifestations of COVID-19



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## List of Abbreviations

ACE2	Angiotensin Converting Enzyme 2
ECG	Electrocardiogram
HfpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
RAAS	Renin–angiotensin–aldosterone system
SARS-CoV-2	Severe acute respiratory syndrome coronavirus

## 6.1 Introduction

There is an increased risk of cardiovascular involvement during respiratory viral infections. This has been studied in the context of influenza. Notably, in most influenza epidemics, more patients died of cardiovascular causes compared to pneumonia.<sup>1</sup> In the context of COVID-19, it has become apparent that cardiovascular complication is a major cause of death, particularly in individuals over 65 years of age who are likely to have various comorbidities such as diabetes, hypertension, and obesity. These patients comprise the majority with cardiac involvement during severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection.<sup>2</sup> This chapter will discuss the various cardiovascular manifestations of COVID-19, including cardiac inflammation, heart failure, stress cardiomyopathy, and hypercoagulability. Additionally, the role of angiotensin converting enzyme 2 (ACE2) will be addressed, as well as possible long-term cardiovascular sequelae that may result from SARS-CoV-2 infection.

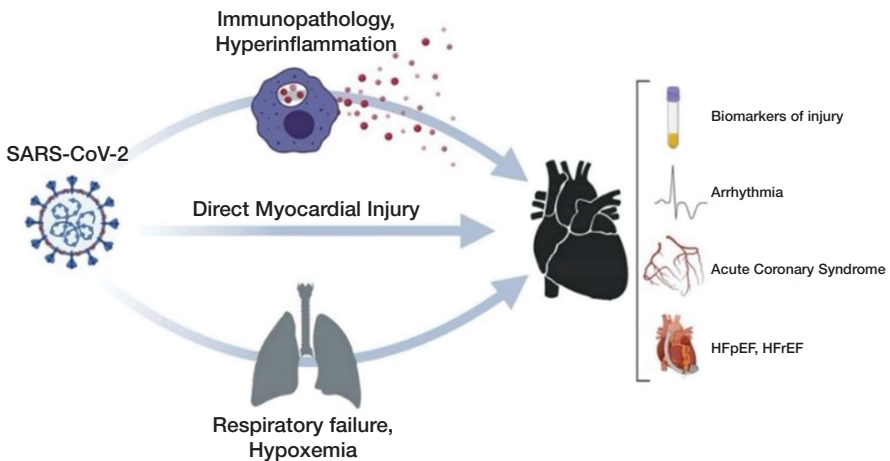
## 6.2 Epidemiology

In a study of 52 critically ill patients with COVID-19, it was found that 40% of patients had comorbidities such as cardiovascular disease, chronic cardiac disease, and cerebrovascular disease.<sup>3</sup> Specifically, more non-survivors of COVID-19 in this

study had preexisting cardiovascular disease (53% vs. 20% in survivors) and preexisting cerebrovascular disease (22% vs. 0% in survivors). Additionally, among the 52 critically ill patients, cardiac injury, indicated by increased levels of troponin I, was reported in 23% of cases.<sup>3</sup> Non-survivors also showed higher rates of heart failure and acute cardiac injury, when compared to survivors of COVID-19.<sup>3</sup> After taking all of these statistics into consideration, it is apparent that the cardiovascular system is significantly affected during SARS-CoV-2 infection, and it is clear that having preexisting cardiovascular conditions places individuals at a significant risk to poor outcomes in the face of COVID-19.

Another study found similar results, in which cardiovascular disease was more prevalent in patients who died due to COVID-19 than patients who survived.<sup>4</sup> Additionally, patients who died had higher levels of troponin, myoglobin, C-reactive protein, serum ferritin, and interleukin-6. Such findings are suggestive of a high inflammatory burden in COVID-19 patients and a possible rise in myocarditis-related cardiac events.<sup>4</sup>

While the mechanism of cardiac injury is not well established, there are a few factors that could be contributing to such injury. First, there is likely an increase in cardiac demand due to the respiratory failure and hypoxemia that commonly occur during COVID-19.<sup>5</sup> Second, it is possible that a direct cardiac injury by SARS-CoV-2 occurs. Third, there could be an indirect cardiac injury from the systemic inflammatory response elicited during SARS-CoV-2 infection.<sup>5</sup> And lastly, the stress of COVID-19 may destabilize any preexisting cardiovascular pathologies.<sup>5</sup> All four possible modalities of cardiac injury can result in arrhythmias, heart failure, or myocardial infarction (Figure 6.1).



**Figure 6.1** COVID-19 cardiac effects

### 6.3 The Role of ACE2 in the Cardiovascular System during COVID-19

It is well known that SARS-CoV-2 infects cells via the ACE2 receptor. Thus, with the abundant ACE2 expression in heart, it seems to be at an increased risk of infection.<sup>6</sup> Notably, SARS-CoV-2 downregulates ACE2 expression, which contributes to myocardial dysfunction. This effect has been observed in ACE2-knockout mice exhibiting severe left ventricular dysfunction.<sup>7</sup> Normally, ACE2 degrades angiotensin II to generate angiotensin, <sup>1-7</sup> which has vasodilatory and antiproliferative effects. Such effects along with anti-angiotensin II action prevent pathologic remodeling of the heart during heart failure and myocardial infarction.<sup>8</sup>

There is a significant controversy surrounding the use of renin–angiotensin–aldosterone system (RAAS) antagonists, strong influencers on the cardiovascular system, during COVID-19. These medications have been found to increase ACE2 expression in many animal studies. While such an increase in humans is helpful in cardiovascular disease, it can theoretically increase susceptibility to SARS-CoV-2. However, the directionality of this effect is debated.<sup>9,10</sup> In a study of 8900 patients with COVID-19, there was no association with the use of RAAS antagonists and increased in-hospital mortality.<sup>11</sup> Thus, it is currently not recommended that ACE inhibitor and ARB therapy, two different modalities of RAAS antagonism, be stopped.<sup>11</sup>

### 6.4 Cardiac Inflammation due to SARS-CoV-2

Viral infections are known to commonly cause myocarditis and pericarditis. In some cases, this can be due to viruses exhibiting molecular mimicry, a phenomenon where viral antigens share features with myocyte and/or pericardial cell antigens.<sup>12</sup> It is possible that SARS-CoV-2 exhibits molecular mimicry. In fact, autopsies of patients who had confirmed COVID-19 show inflammatory infiltrates composed of macrophages and CD4 T cells. These mononuclear infiltrates were associated with regions of cardiomyocyte necrosis.<sup>13</sup> While such indications of myocardial inflammation are present, there has been no data to suggest the presence of SARS-CoV-2 within myocardial tissue itself. Such a finding would support the idea of SARS-CoV-2 exhibiting molecular mimicry.

The clinical presentation of myopericarditis in COVID-19 can be similar to that of myocardial infarction. Chest discomfort and fatigue have been primarily observed.<sup>14</sup> In terms of diagnostic testing, ST elevation on electrocardiogram (ECG) is a key finding, as well as increased levels of troponin T indicative of myocardial damage.<sup>14</sup> Both of these findings are also observed in myocardial infarction. In a case study from Italy, a 53-year-old patient with myopericarditis had no signs or symptoms of severe lung disease.<sup>14</sup> The patient had only complained of a dry cough and fatigue in the week preceding her symptoms related to myopericarditis. So it is apparent that inflammation of the heart can occur even in seemingly less severe cases of COVID-19.

## 6.5 Heart Failure due to SARS-CoV-2

Heart failure is another significant cardiac manifestation of COVID-19.<sup>5</sup> Specifically, heart failure can occur in the setting of SARS-CoV-2-induced myocarditis. However, it is unclear whether SARS-CoV-2-induced myocarditis more commonly results in heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF). Though, since most patients with uncomplicated lymphocytic myocarditis present with normal heart function, this may indicate that HFpEF is more common.<sup>15</sup> It is notable that since COVID-19 cases are highly contagious, an echocardiograph is risky to obtain so the status of left ventricular function may not be fully established in these patients.

Heart failure can also occur in the setting of arrhythmia, which has been reported frequently in COVID-19 cases.<sup>16</sup> Without an adequately functioning cardiac conduction system, the heart is unable to pump blood effectively, thus resulting in heart failure. It is noteworthy that while arrhythmia can cause heart failure, it can also be a result of heart failure. Such a distinction is important when considering treatment options for the patient.

## 6.6 Stress Cardiomyopathy due to SARS-CoV-2

Stress, or takotsubo, cardiomyopathy is a condition that primarily affects women and can occur after a significant physical or emotional stressor.<sup>17, 18</sup> Viral infection has been found to trigger stress cardiomyopathy in some cases.<sup>19</sup> In COVID-19, high inflammatory burden is a plausible trigger for this cardiac condition, and there have been a few case reports of women exhibiting this illness.<sup>20, 21</sup> Although this condition is rarer than those already discussed, it is worth noting some of its key findings.

Patients with stress cardiomyopathy have cardiac wall motion abnormalities that are apparent during echocardiography. Additionally, a low left ventricular ejection fraction is observed in this condition—one much lower than that of acute coronary syndrome.<sup>17</sup> It is important to differentiate stress cardiomyopathy from myocardial infarction, especially since the ECG findings for both conditions can be very similar.<sup>20</sup> Treatment for stress cardiomyopathy is conservative, and many patients, including one of the COVID-19 patients with this condition, recover left ventricle function without invasive coronary procedures.<sup>20</sup> A close monitoring is essential nonetheless, since a declining left ventricle function can result in heart failure.<sup>20</sup>

## 6.7 Vascular Manifestations of COVID-19

There are a few possible mechanisms through which the vascular system is damaged in the setting of COVID-19. These mechanisms are similar to those likely affecting the cardiac system. One possibility is that the damage caused by the virus in the lungs can result in hypoxia of the blood vessels and resulting vascular injury.<sup>22</sup> Another possibility is that many ACE2 receptors in the vascular systems are prone to an increased risk of SARS-CoV-2 infection.<sup>6</sup> Lastly, since COVID-19 affects many different organ

systems and promotes an inflammatory state, the vasculature can get damaged as a direct consequence of this state.<sup>22</sup> Damage to the vasculature caused by any of these three mechanisms can lead to abnormal activation of the coagulation cascade. Many COVID-19 patients have an increased D-dimer level, indicative of increased clot formation.<sup>16</sup> These patients have an increased likelihood of death during infection.<sup>22</sup> Additionally, it is notable that individuals with preexisting conditions that significantly affect the blood vessels, such as hypertension and diabetes, tend to be at a greater risk of SARS-CoV-2 infection and have poor outcomes during infection.<sup>22</sup>

A hypercoagulable state, indicated by an increased levels of D-dimer and fibrinogen, is common during COVID-19.<sup>23</sup> In such a state, patients are at an increased risk of pulmonary embolism, deep vein thrombosis, stroke, and disseminated intravascular coagulation. All of these conditions can be extremely debilitating and potentially fatal. In fact, many COVID-19 patients in their 30s or 40s have presented with a stroke due to this hypercoagulable state.<sup>24</sup> This is particularly alarming since the median age for severe stroke is 74.<sup>24</sup> Therefore, it is important for clinicians to monitor all patients regardless of age, for the conditions caused by hypercoagulability.

### 6.8 Possible Long-Term Cardiovascular Implications Following COVID-19

While the acute cardiovascular manifestations of COVID-19 are clear in their clinical presentation as discussed above, it is important to keep in mind cardiovascular complications that are possible even after recovery from acute illness. Figure 6.2 depicts the concept that once the acute phase of the illness has resolved, the long-term complications may arise in the convalescent and chronic phases of disease, long after viral

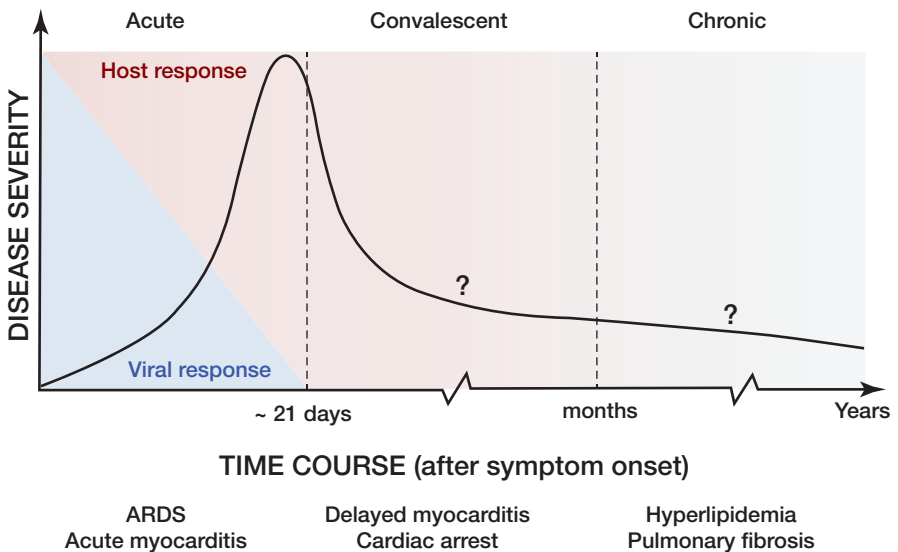


Figure 6.2 Long-term sequelae of COVID-19



clearance has been achieved. In some case reports from Italy, fulminant myocarditis has been described to persist even after the resolution of acute respiratory symptoms.

While COVID-19 is a nascent pandemic, long-term sequelae are unknown, but we can learn from the SARS-CoV experience. In a study of 25 individuals who had recovered from SARS-CoV infection 12 years ago, 68% had hyperlipidemia and 44% had cardiovascular abnormalities in the 2017 study.<sup>25</sup> Additionally, it was found that the lipid metabolisms of these individuals were significantly altered when compared to normal controls, resulting in increased levels of serum lipids and free fatty acids.<sup>25</sup> Such a hyperlipidemic state places these recovered SARS-CoV patients at an increased risk for conditions such as atherosclerosis and myocardial infarction. Since SARS-CoV-2 is similar to SARS-CoV, it is possible that it will cause similar long-term cardiovascular effects. It will be important in the future for clinicians to keep such effects in mind as more people get infected with COVID-19 during the pandemic.

## 6.9 Conclusion

It is clear that the cardiovascular system is not spared during SARS-CoV-2 infection. In particular, individuals over 65 years of age with preexisting comorbidities such as diabetes, hypertension, and obesity are at an increased risk of severe cardiovascular complication.<sup>2</sup> Common cardiovascular complications include myocardial infarction, heart failure, cardiac inflammation, arrhythmia, and hypercoagulability. A less common cardiovascular complication is stress cardiomyopathy. In addition to the acute cardiovascular conditions that occur during COVID-19, it is important to also consider the long-term complications that may arise. After the SARS-CoV experience that occurred 12 years ago, many patients who survived infection had altered lipid metabolism resulting in hyperlipidemia, a state known to increase the risk of atherosclerosis and myocardial infarction.<sup>25</sup> Since SARS-CoV-2 shares characteristics with SARS-CoV, the long-term sequelae that affected SARS-CoV patients may also affect SARS-CoV-2 patients many years from now.

### Key Learning Points

1. Around one-third of COVID-19 patients have been found to develop cardiovascular complications.
2. The pathophysiology as to how the cardiovascular system is involved during SARS-CoV-2 infection is complex and multifactorial.
3. Older patients with comorbidities are likely to suffer from acute atherosclerotic complications.
4. Younger and healthy patients rarely may develop acute fulminant myocarditis leading to acute cardiac decompensation and malignant arrhythmia resulting in sudden death.
5. The COVID-19 pandemic has changed the way cardiology is routinely practiced.

**Summary of Cardiovascular Findings in COVID-19**

Cardiovascular Complications	Pathophysiology
Myopericarditis	Possible molecular mimicry exhibited by SARS-CoV-2 results in inflammation of the heart
Heart failure	Preserved ejection fraction heart failure occurs due to myocarditis Heart failure can also occur due to arrhythmia secondary to cardiac injury Stress cardiomyopathy can result in heart failure as well
Arrhythmia	Arrhythmia can be due to heart failure, myocarditis, or the cardiac injury that occurs in SARS-CoV-2 infection
Myocardial infarction	Myocardial infarction can occur due to the cardiac injury caused by SARS-CoV-2 infection
Stress cardiomyopathy	Physiologic stress (high inflammatory burden, hypoxia, etc.) due to SARS-CoV-2 infection results in stress cardiomyopathy
Pulmonary embolism, stroke, deep vein thrombosis, and disseminated intravascular coagulation	Vascular injury caused by SARS-CoV-2 results in a hypercoagulable state that has been found in many COVID-19 patients (indicated by elevated fibrinogen and D-dimer)

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# Central Nervous System (CNS) Manifestations of COVID-19

## CHAPTER 07

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### List of Abbreviations

ANE	Acute necrotizing encephalitis
ARDS	Acute respiratory distress syndrome
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
EMG	Electromyography
ER	Emergency room
LVO	Large vessel occlusion
MERS	Middle East respiratory syndrome
MRI	Magnetic resonance imaging
PNS	Peripheral nervous system
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus

### 7.1 Introduction

There have been several reported cases that have demonstrated that infection by severe acute respiratory syndrome coronavirus (SARS-CoV-2) can have neurological manifestations ranging from mild to severe symptoms and may also involve the central nervous system (CNS), peripheral nervous system (PNS), and or skeletal muscle. Among the most common neurological manifestations of SARS-CoV-2 is the loss of sense of taste and/or smell typically by the third day.<sup>1</sup> It is important to know that patients may present with neurological symptoms as the first or only sign of the SARS-CoV-2 infection. This chapter discusses the common and rare neurological manifestations of SARS-CoV-2 that have been reported so far.

## 7.2 How SARS-CoV-2 Can Infect the Nervous System

Although the exact manner with which SARS-CoV-2 acts on the nervous system has yet to be found, there are a few probable explanations. The ACE2 receptor has been identified as the primary receptor involved with the SARS-CoV-2 virus. Because this receptor is expressed in skeletal muscles and throughout the nervous system, they can be considered as capable of being infected by the SARS-CoV-2 virus via either direct or indirect methods.<sup>2</sup>

Autopsies of COVID-19-positive patients demonstrated brain tissue that was hyperemic and edematous, and had degenerated neurons.<sup>2</sup> It is also probable for SARS-CoV-2 to infect the CNS by dissemination of SARS-CoV-2 through the olfactory bulb and cribriform plate or due to hematogenous spread of the virus from systemic to cerebral circulation.<sup>3</sup> Previous coronavirus infections, like SARS-CoV, have demonstrated neurological manifestations of the virus.<sup>4</sup> Autopsies of patients infected with SARS-CoV detected the presence of SARS-CoV nucleic acid in the cerebrospinal fluid (CSF) and brain tissue.<sup>2</sup> Previous studies showed that SARS-CoV-infected patients had developed rhabdomyolysis, myopathy, and seizures.<sup>5</sup> There were also reports of Middle East respiratory syndrome (MERS) patients during the MERS outbreak developing neurological symptoms of confusion and seizures.<sup>5</sup>

The first reported neurological study in Wuhan, China,<sup>2</sup> examined 214 consecutive COVID-19-positive patients (mean age of 52.7 years)<sup>3</sup> who were treated at three different hospitals from January 16 to February 19, and their illness was categorized by severity based on the American Thoracic Society guidelines for *community-acquired pneumonia* (Table 7.1). According to these guidelines, 41.1% (88) of patients had “severe infection” and 58.9% (126) of patients had “nonsevere infection.” Neurological symptoms were categorized into four categories:

**Table 7.1** Key Neurological Findings from the Study: Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China<sup>2</sup>

Summary of Key Neurological Findings
19/214 COVID-19 patients had PNS manifestations 12 had impaired taste 11 had impaired smell 3 had impaired vision
53/214 COVID-19 hospitalized patients had CNS manifestations 35 had dizziness 28 had headache 16 had impaired consciousness 6 had acute cerebrovascular disease 1 had ataxia 1 had seizure
23/214 COVID-19 hospitalized patients had skeletal muscle injury

- CNS: headache, dizziness, altered consciousness
- PNS: nerve pain and loss of senses of smell, taste, and/or vision
- Cerebrovascular disease: seizure, stroke, ataxia
- Skeletal muscle symptoms.

Of the 214 patients, 36.4% had neurologic manifestations (ie, CNS, PNS, skeletal muscle). Patients with severe infection were more likely to be older and have hypertension and had fewer typical COVID-19 symptoms (cough, fever) compared to those with nonsevere infection, and patients with severe infection were more likely to develop neurologic manifestations compared to those with nonsevere infection.<sup>2</sup> 38.8% (83) had one or more comorbidity; hypertension, diabetes, cardiac or cerebrovascular disease, malignancy, or chronic kidney disease. Such neurological symptoms mostly manifested in the early period of the illness (the median time to hospital admission 1–2 days).<sup>2</sup>

### 7.3 Cerebrovascular Disease

There have been reports of strokes in patients who have tested positive for COVID-19 and particularly in younger patients, patients younger than 50 years of age, when patients who typically get strokes are 74+ years.<sup>6</sup> Based on the laboratory studies of COVID-19-positive patients done so far, it is known that COVID-19 is frequently associated with increased D-dimer levels. Increased D-dimer levels may be indicative of blood clots through detecting an irregularly high amount of fibrin degradation material.<sup>7</sup> Blood clots have been seen as a very concerning symptom of COVID-19, and it is believed that the SARS-CoV-2 is infecting blood vessels<sup>8</sup>. One study demonstrated how SARS-CoV-2 had infected the endothelial cells lining the inside of blood cells.<sup>8</sup> Blood clotting is especially problematic in patients in critical condition, those who are immobilized, and those with preexisting conditions that already put strain on the involved systems such as diabetes and hypertension.

Some patients are presenting with stroke as the first symptom of COVID-19 and these strokes are also appearing in COVID-19-positive patients with no known heart conditions or no other underlying illnesses such as hypertension or diabetes.<sup>9</sup> In the Wuhan study, 14 strokes out of 214 COVID-19-positive patients.<sup>3</sup>

In a study of 10 COVID-19-positive patients with an age range of 25–75 years who had suffered from an ischemic stroke, 80% had preexisting conditions such as diabetes or hypertension but none had preexisting cerebrovascular disease, coronary disease, or atrial fibrillation.<sup>10</sup> Patients showed increased laboratory values of D-dimer; 80% of these patients also presented to the emergency room (ER) initially with neurological symptoms rather than respiratory symptoms, two passed away from stroke, two passed away from the coronavirus attacking their lungs, and one was in critical condition due to acute respiratory distress syndrome (ARDS).<sup>10</sup> Patients had either branch emboli, small vessel, or large vessel occlusion (LVO).<sup>10</sup> There were five patients who had LVO, three of whom ended in mortality and one

of whom was the patient in critical condition due to ARDS.<sup>10</sup> Patients with LVO were associated with either cardioembolism or hypercoagulable state.<sup>10</sup>

A retrospective cohort study published on May 13, 2020, in stroke examined all patients admitted for stroke between March 15, 2020, and April 19, 2020, across New York University Langone Hospital locations in Brooklyn, Long Island, and Manhattan.<sup>11</sup> They were divided into three groups: patients who had ischemic stroke and were simultaneously COVID-19-positive, the contemporary controls who were patients who had ischemic stroke and did not have COVID-19, and the historical controls which were patients who had ischemic stroke and who were discharged from the hospital system between March 15, 2019, and April 15, 2019.<sup>11</sup> The results showed that only 32 (0.9%) of the 3556 hospitalized COVID-19-positive patients had imaging-confirmed ischemic strokes with 63 years of age being the median age of the 32 patients and 71.9% being men.<sup>11</sup> More studies are needed to clarify if there is an association between SARS-CoV-2 and ischemic stroke (Table 7.2).

**Table 7.2** Cases of Stroke Associated with SARS-CoV-2

Study	Key Neurological Findings
Etiologic subtypes of ischemic stroke in SARS-COV-2 virus patients <sup>10</sup>	<p><i>Findings</i></p> <p>10 COVID-19 hospitalized patients with an age range of 25–75 had suffered ischemic stroke from four centers in New York city</p> <ul style="list-style-type: none"> <li>All patients had increased values of D-dimer levels</li> <li>Seven had diabetes</li> <li>Six had hypertension</li> <li>One developed atrial fibrillation during their time in the hospital</li> <li>Eight presented to the ER initially with neurological complaint</li> <li>Four passed away</li> <li>One was in critical condition because of ARDS</li> </ul>
SARS2-CoV-2 and Stroke in a New York Health-Care System <sup>11</sup>	<p><i>Findings</i></p> <p>32 of 3556 hospitalized COVID-19-positive patients across three New York hospitals between 3/15/19 &amp; 4/15/19 had imaging-confirmed ischemic strokes</p> <ul style="list-style-type: none"> <li>Median age: 63 years</li> <li>71.9% were men</li> </ul>
Large artery ischemic stroke in severe acute respiratory syndrome (SARS) <sup>12</sup>	<p><i>Findings</i></p> <p>5 of 206 COVID-19 hospitalized patients in Singapore had large vessel strokes</p> <ul style="list-style-type: none"> <li>Four were in critical condition</li> <li>Three passed away</li> </ul>
COVID-19 presenting as stroke <sup>13</sup>	<p><i>Findings</i></p> <p>Four PCR-confirmed COVID-19 patients had imaging-confirmed stroke in this retrospective study</p> <ul style="list-style-type: none"> <li>All four presented stroke as the initial symptom</li> <li>All four patients were in the age range of 73–88 years</li> </ul>

## 7.4 Acute Encephalitis and Meningitis

Henry Ford Health System reported one case of a 58-year-old woman developing a rare form of encephalitis called acute necrotizing encephalitis, or (ANE), reported in the journal *Radiology*.<sup>14</sup> She initially presented with fever, cough, and muscle aches, but then later she presented to the ER with confusion and altered mental status.<sup>14</sup> A rapid COVID-19 test made in-house confirmed COVID-19 infection when the flu test came out negative.<sup>14</sup> CT (computed tomography) and MRI (magnetic resonance imaging) scans confirmed the ANE diagnosis. Acute necrotizing encephalopathy, also known as acute necrotizing encephalopathy of childhood, is a rare type of encephalopathy characterized by multiple bilateral brain lesions.<sup>15</sup> It was first discovered in Eastern pediatric populations in 1995 but is rare in western countries and adult populations.<sup>16</sup>

Another report described a case of a 24-year-old man who was infected with SARS-CoV-2 and developed meningoencephalitis.<sup>17</sup> He presented with a fatigue and fever on day 1, sought a doctor on day 2, and was prescribed laninamivir and antipyretic agents because of clinical symptoms; on day 5, his symptoms worsened with the addition of sore throat and headaches; and on day 9, he was found unconscious and rushed to the hospital by ambulance.<sup>17</sup> He had generalized seizures for a minute and at the hospital tested negative for SARS-CoV-2 using the nasal swab test, but tested positive for SARS-CoV-2 in his CSF.<sup>17</sup> Brain MRIs were taken 20 hours after admission demonstrating right lateral ventriculitis and encephalitis on the right mesial lobe of the hippocampus with a differential diagnosis of hippocampal sclerosis.<sup>17</sup>

There has been one case so far of meningitis seen in a 5-year-old girl. She was complaining of a headache and had a fever for about a month and had tested positive for COVID-19. The child then developed meningitis and spent 2 weeks on a ventilator before passing away. She was taken off the ventilator after she was no longer improving and physicians believed she was brain dead.<sup>18</sup>

A study of HCV-OC42 examines whether a respiratory virus can infect the CNS and cause brain inflammation.<sup>3</sup> Because there have not been many cases of SARS-CoV-2 being tied to meningitis and/or encephalitis, more studies need to be done in order to substantiate this relationship (Table 7.3).

## 7.5 Headaches

Patients who are positive for COVID-19 have presented with headaches as a symptom of the virus.<sup>3</sup> In the meningitis case of the 5-year-old girl, she initially presented with headaches as the only symptom of COVID-19 for a month.<sup>18</sup>

However, this appears to be an isolated occurrence. Therefore, headaches may be a result of the systemic disease rather than a direct invasion of the CNS by the virus, and this is especially likely in patients who have no other neurological symptoms.<sup>3</sup>



**Table 7.3** Cases of Encephalitis Tied to SARS-CoV-2

Study	Key Neurological Findings
COVID 19 linked to rare form of encephalitis <sup>14</sup>	Case report: Acute necrotizing encephalitis Age: 58 years old Sex: Female 3 days of fever, cough, muscles aches and altered Altered mental status Tested positive for SARS-CoV-2 on a rapid COVID-19 test
A first case of meningitis/ encephalitis associated with SARS-coronavirus-2 <sup>17</sup>	Case report: Meningoencephalitis Age: 24 years old Sex: Male Tested positive for SARS-CoV-2 using reverse transcription polymerase chain reaction (RT-PCR) Analysis of CSF Tested negative for SARS-CoV-2 using RT-PCR Analysis using nasopharyngeal swab test
5-year-old with rare complication becomes first Michigan child to die of COVID-19 <sup>18</sup>	Case report: Meningitis Age: 5 years old Sex: Female

## 7.6 Peripheral Nervous System Manifestations

Some PNS manifestations of COVID-19 include impaired sense of taste, sense of smell, vision, and polyneuropathy. There have been reports that previous coronaviruses, such as SARS-CoV and MERS, had PNS manifestations such as weakness and decreased deep tendon reflexes.<sup>3</sup>

According to the Wuhan study, there were no significant differences in the laboratory studies between patients with and without PNS manifestations, and there were no significant differences between those patients with PNS systems and severe infection and those with PNS manifestations and without severe infection.<sup>2</sup>

There have been 12 reported cases of Guillain–Barrésyndrome in COVID-19-positive patients.<sup>3</sup> Guillain–Barrésyndrome is a rare disorder where the body’s immune system attacks its nerves.<sup>19</sup> It can cause muscle weakness and occasionally, paralysis.<sup>19</sup> Of these 12 patients, 5 were from Northern Italy and they all developed Guillain–Barrésyndrome after the onset of COVID-19 and systemic manifestations of COVID-19.<sup>20</sup> At the onset of their neurological symptoms, 4 out of these 5 patients tested positive on the SARS-CoV-2 nasopharyngeal swab test and 1 tested negative.<sup>20</sup> Four patients developed weakness in their lower extremities and facial diplegia, and one patient developed paresthesia and ataxia.<sup>20</sup> Over a 3- to 4-day period, four of the patients also developed generalized, flaccid tetraparesis, or tetraplegia, and three of whom received mechanical ventilation.<sup>20</sup>

These patients showed first symptoms of Guillain–Barrésyndrome 5–10 days after first onset of symptoms of COVID.<sup>20</sup> Among the other 7 of the 12 patients,

there were instances of patients presenting with neurological manifestations prior to COVID-19 diagnosis. Several of these patients had also developed systemic manifestations, such as fever and cough, and ground-glass lung opacities in either one or both lungs either before or after developing neurological manifestations. There have also been cases of patients who were infected with MERS-CoV and patients who have been infected with HCV-OC43 and who have also developed Guillain–Barré syndrome.<sup>17</sup> These are only a few cases so more research needs to be done in order to substantiate that there is a relationship between SARS-CoV-2 and Guillain–Barré syndrome (Table 7.4).

**Table 7.4** Cases of Guillain–Barré Syndrome Tied to SARS-CoV-2

Patient	Age	Sex	Initial Presentation	Timeline
Neurologic symptoms and COVID-19: What’s known, what isn’t <sup>21</sup>	61 y.o.	F	Autoimmune neuropathy	<p><i>Day 8 of hospitalization</i></p> <ul style="list-style-type: none"> <li>Developed dry cough, fever, ground-glass lung opacities</li> </ul> <p><i>Day 30 of hospitalization</i></p> <ul style="list-style-type: none"> <li>Discharged from hospital after recovering</li> </ul>
COVID-19 may induce Guillain–Barré syndrome <sup>22</sup>	64 y.o.	M	Presented to hospital after falling & tearing rotator cuff	<p><i>Day 1 of symptoms</i></p> <ul style="list-style-type: none"> <li>2 days prior to hospital presentation</li> <li>Fever and cough</li> <li>Nasal swab test was positive for SARS-CoV-2</li> </ul> <p><i>Day 5 of symptoms</i></p> <ul style="list-style-type: none"> <li>Fever subsided</li> </ul> <p><i>Day 10 of symptoms</i></p> <ul style="list-style-type: none"> <li>Developed paresthesias in feet and hands</li> </ul> <p><i>Day 13 of symptoms</i></p> <ul style="list-style-type: none"> <li>Flaccid severe tetraparesia</li> </ul> <p><i>Neurological evaluation</i></p> <ul style="list-style-type: none"> <li>MRC (power muscle strength) evaluation</li> <li>2/5 in the legs</li> <li>2/5 the arms</li> <li>3/5 in the forearms</li> <li>4/5 in the hands</li> </ul>
Guillain–Barré syndrome associated with COVID-19 infection: a case report <sup>23</sup>	65 y.o.	M	Presented to the ER with symptoms of acute progressive symmetric ascending quadriparesis	<p><i>2 weeks prior to ER admission</i></p> <ul style="list-style-type: none"> <li>Fever, cough, and occasional dyspnea</li> <li>COVID-19 was diagnosed via oropharyngeal sampling and reverse transcription-polymerase test</li> <li>Treated with hydroxychloroquine, lopinavir/ritonavir, and azithromycin</li> </ul>

(continued)

**Table 7.4** (continued)

Patient	Age	Sex	Initial Presentation	Timeline
			<p><i>Past medical history</i></p> <p>Type 2 diabetes mellitus</p> <ul style="list-style-type: none"> <li>• Takes metformin</li> </ul>	<p><i>5 days prior to ER admission</i></p> <ul style="list-style-type: none"> <li>• Acute progressive weakness of distal extremities, bilateral facial paresis</li> </ul> <p><i>Neurological evaluation</i></p> <ul style="list-style-type: none"> <li>• MRC strength evaluation</li> <li>• 2/5 in the legs</li> <li>• 1/5 in thighs</li> <li>• 3/5 the arms</li> <li>• 2/5 in the forearms</li> <li>• Generally absent deep tendon reflexes</li> <li>• Reduced fine touch sensation and vibration distal to the ankle</li> <li>• House-Brackmann grade 3 bifacial nerve palsy</li> <li>• No spine sensory level</li> </ul>
Covid-19 and Guillain-Barré syndrome: more than a coincidence! <sup>24</sup>	70 y.o.	F	<p>Bilateral weakness and tingling in all 4 extremities within a time period of 48 h</p> <p><i>Past medical history</i></p> <p>Rheumatoid arthritis (RA) for which she was taking 7.5 mg prednisone</p>	<p><i>3 days prior to neurological symptoms onset</i></p> <ul style="list-style-type: none"> <li>• Dry cough resolving on its own within 48h</li> </ul> <p><i>Days 1 and 2 of neurological symptoms</i></p> <ul style="list-style-type: none"> <li>• Bilateral weakness and tingling in all four extremities</li> <li>• Diagnosed with RA exacerbation and given corticosteroids</li> </ul> <p><i>Day 10 of neurological symptoms</i></p> <ul style="list-style-type: none"> <li>• Tested positive for SARS-CoV-2 on RT-PCR</li> <li>• Oropharyngeal test</li> <li>• Admitted to neurology department of hospital</li> </ul> <p><i>Neurology examination</i></p> <ul style="list-style-type: none"> <li>• Quadriplegia</li> <li>• Hypotonia</li> <li>• Areflexia</li> <li>• Bilateral positive Lasègue sign</li> <li>• Nerve conduction study showed all fourlimbs had a significant reduction/absence of electrical potentials in both sensory and motor nerves</li> <li>• Needle electromyography (EMG) showed a significant amount of fibrillation potentials at rest</li> <li>• Chest CT: ground-glass appearance of left lung</li> </ul>

**Table 7.4** (continued)

Patient	Age	Sex	Initial Presentation	Timeline
				<p><i>Treatment:</i></p> <ul style="list-style-type: none"> <li>• IV immunoglobulin (2g/kg for 5 days)</li> <li>• Hydroxychloroquine (600 mg/day)</li> <li>• Azithromycin (500 mg for the first day then 250 mg/day)</li> </ul> <p><i>Day 20 of neurological symptoms</i></p> <ul style="list-style-type: none"> <li>• No significant improvement in the condition</li> </ul>
Guillain–Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? <sup>25</sup>	61 y.o.	F	Acute weakness in bilateral lower extremities and severe fatigue that progressed within 1 day	<p><i>Day 1 of hospital admission</i></p> <ul style="list-style-type: none"> <li>• Neurological examination</li> <li>• MRC strength evaluation</li> <li>• 4/5 in both legs and feet</li> <li>• Areflexia in both legs</li> </ul> <p><i>Day 3 of hospital admission</i></p> <ul style="list-style-type: none"> <li>• MRC strength evaluation</li> <li>• 3/5 in both legs and feet</li> <li>• 4/5 in both arms and hands</li> </ul> <p><i>Day 4 of hospital admission</i></p> <ul style="list-style-type: none"> <li>• Thrombocytopenia, lymphocytopenia, and increased protein levels</li> </ul> <p><i>Day 5 of hospital admission</i></p> <ul style="list-style-type: none"> <li>• Nerve conduction studies showed signs of demyelinating neuropathy</li> </ul> <p><i>Day 8 of hospital admission</i></p> <ul style="list-style-type: none"> <li>• Diagnosed with Guillain–Barré syndrome</li> <li>• Developed a fever and dry cough</li> <li>• Chest CT showed ground-glass opacities in both lungs</li> <li>• Tested positive for SARS-CoV-2 on RT-PCR</li> <li>• Oropharyngeal test</li> <li>• Treatment</li> <li>• Given IV immunoglobulin and Antiviral drugs (ritonavir, arbidol, and lopinavir) for supportive care</li> </ul> <p><i>Day 20 of hospital admission</i></p> <ul style="list-style-type: none"> <li>• Patient’s condition improved with normal lymphocyte and thrombocyte levels were normal</li> </ul> <p><i>Day 30 of hospital admission</i></p> <ul style="list-style-type: none"> <li>• Discharged with normal muscle strength in all extremities, normal tendon reflexes, no respiratory symptoms, and tested negative on SARS-CoV-2 oropharyngeal</li> </ul>

## 7.7 Skeletal Muscle Injury

According to the laboratory values from the Wuhan study, patients who had skeletal muscle injury had significantly higher levels of creatine kinase compared to those who had no skeletal muscle injury regardless of the disease severity.<sup>2</sup> The laboratory values of patients with skeletal muscle injury showed an evidence of an increased inflammatory response through increased neutrophil counts, lower lymphocyte counts, and greater C-reactive protein levels, and also showed an evidence of possible blood coagulation dysfunction through the increased D-dimer levels.<sup>2</sup> The laboratory values of patients who had skeletal muscle injury also showed an evidence of damage to multiple organs: liver (increased lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase where the levels in patients with severe infection were significantly higher than the levels of those with nonsevere infection) and kidney abnormalities (increased levels of blood urea nitrogen where the blood urea nitrogen levels were significantly higher in patients with severe infection than in those with nonsevere infection and increased levels of creatine).<sup>2</sup>

## 7.8 Conclusion

1. Patients diagnosed with COVID-19 can develop neurological manifestations that can affect the CNS or PNS or cause skeletal muscle injury.
2. Patients may present with neurological manifestation prior to COVID-19 diagnosis and/or without displaying any of the symptoms typical to COVID-19 such as fever and cough.
3. Possible CNS manifestations seen so far include headache, dizziness, loss of consciousness, and cerebrovascular disease, and there have only been a few cases of encephalitis and meningitis.
4. Possible PNS manifestations seen so far include the loss of sense of taste, smell, and vision and rare manifestation seen in Guillain–Barré syndrome.
5. Patients infected with the SARS-CoV-2 virus who had no comorbidities or risk factors for cerebrovascular disease have been shown to develop cerebrovascular disease as a neurological manifestation.

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# Gastrointestinal Manifestations of COVID-19

## CHAPTER 08

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### List of Abbreviations

ACG	American College of Gastroenterology
FIT	Fecal immunohistochemistry test
GI	Gastrointestinal
IBD	Inflammatory bowel disease
PPE	Personal protective equipment
PPI	Proton pump inhibitor
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

### 8.1 Introduction

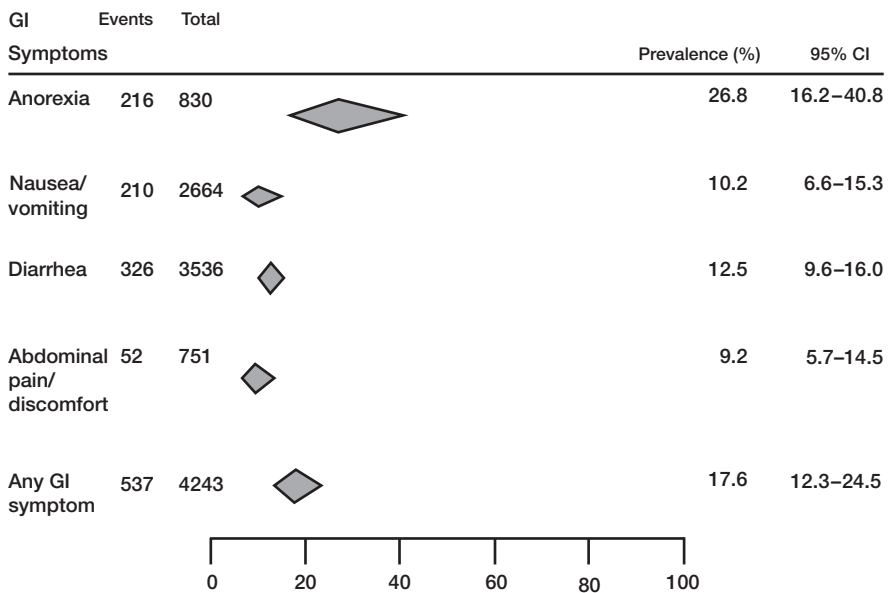
COVID-19 has many gastrointestinal (GI) manifestations, which can present even in the absence of respiratory symptoms, and also has an impact on many GI diseases. Gastroenterology utilizes minimally invasive endoscopic procedures to diagnose, monitor, and treat pancreatic, GI, and hepatobiliary diseases, including GI bleeding, gastroesophageal reflux disease, pancreatitis, inflammatory bowel disease (IBD), celiac disease, cirrhosis, hepatitis, and colorectal cancer. Immunosuppressive agents, including biologic medications and steroids, are used to treat disorders such as IBD and autoimmune hepatitis. Many nonurgent endoscopies were temporarily put on hold from March 2020 through April 2020 due to concerns for SARS-CoV-2 transmission, particularly with aerosol-generating endoscopic procedures and fecal–oral route of viral spread, and to preserve personal protective equipment (PPE) in the setting of widespread shortage. With adequate supplies of proper PPE and decrease in COVID-19 cases, elective outpatient endoscopic procedures resumed in most facilities by late May 2020. This chapter addresses the GI manifestations of COVID-19 and the virus’s impact on various GI diseases and access to endoscopy.



## 8.2 Presentation

Patients infected with SARS-CoV-2 frequently develop, or present with, GI symptoms, such as anorexia, diarrhea, nausea, vomiting, and abdominal pain.<sup>1–3</sup> A figure adapted from a meta-analysis of over 4000 patients positive for COVID-19 showing the distribution of GI symptoms is illustrated in Figure 8.1. Although the prevalence of GI symptoms was low in early studies, there was a large discrepancy between Chinese and non-Chinese studies.<sup>3</sup> One possible explanation of the difference between studies is whether anorexia is included as a GI symptom, as it could be included in other organ systems, and was not reported in many early Chinese studies. When reported, anorexia is often times the most frequently reported GI symptom and may be present in up to 60% of cases.<sup>1,2,4,5</sup> There is a small, but measurable number of cases presenting as acute pancreatitis, which affected Blacks and Hispanics at significantly higher rates, highlighting the racial disparities seen with this disease.<sup>6</sup>

Although respiratory symptoms are the primary presenting symptom of COVID-19, many patients have co-occurring GI symptoms and some patients develop GI symptoms in the absence of respiratory symptoms. In one study of 206 patients with mild COVID, 23% had only digestive symptoms and 33% had a mixture of digestive and respiratory symptoms.<sup>7</sup> Multiple studies have shown that patients with GI symptoms in the absence of respiratory symptoms take longer to present to the hospital, rendering the risk of propagating community viral spread for longer



**Figure 8.1** Prevalence of GI symptoms in COVID-19-positive patients. Adapted from Cheung et al.<sup>1</sup>

periods of time.<sup>1,7</sup> Additionally, these patients may have a longer duration between symptom onset and viral clearance, taking up to an additional 7 days to clear the virus compared to patients with respiratory symptoms.<sup>7</sup> This suggests that GI symptoms should not be overlooked and should prompt a rapid consideration of additional workup and monitoring.

The virus has been isolated from feces of infected persons, and can persist in the stool up to 10 days after resolution of symptoms after it clears the respiratory system, raising concern for possible fecal–oral transmission.<sup>8,9</sup> In fact, some case studies have isolated intact virus in the stool, but direct transmission has not yet been observed.<sup>10</sup>

Patients with COVID-19 often have abnormal liver enzymes which may or may not be present on initial presentation. It has been hypothesized that the development of transaminitis could be related to biology of the virus, which enters cells via the angiotensin-converting enzyme 2 membrane protein receptor and is highly expressed in the colon, liver, and cholangiocytes<sup>11</sup>; however, there are various other possible etiologies which will be discussed later in this chapter.

### 8.3 Endoscopy and Risk of Transmission

Gastroenterologists routinely perform aerosol-generating procedures, including esophagogastroduodenoscopy, colonoscopy, sigmoidoscopy, small bowel enteroscopy, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, and esophageal manometry.<sup>12</sup> The risk of viral transmission during upper endoscopies is of particular concern as viral particles may become aerosolized during the insertion of the endoscopy into the pharynx (triggering the gag reflex) and from the endoscope's working channel as instruments are inserted and removed.<sup>12</sup> During the surge of the COVID-19 pandemic, elective procedures (colon cancer screening, GI motility testing, variceal surveillance, etc.) were delayed due to the concern for SARS-CoV2 transmission. When urgent/emergent procedures were performed (symptomatic GI bleeding, dysphagia significantly impacting oral intake, cholangitis, GI obstruction), the following procedural precautions were recommended:<sup>12</sup>

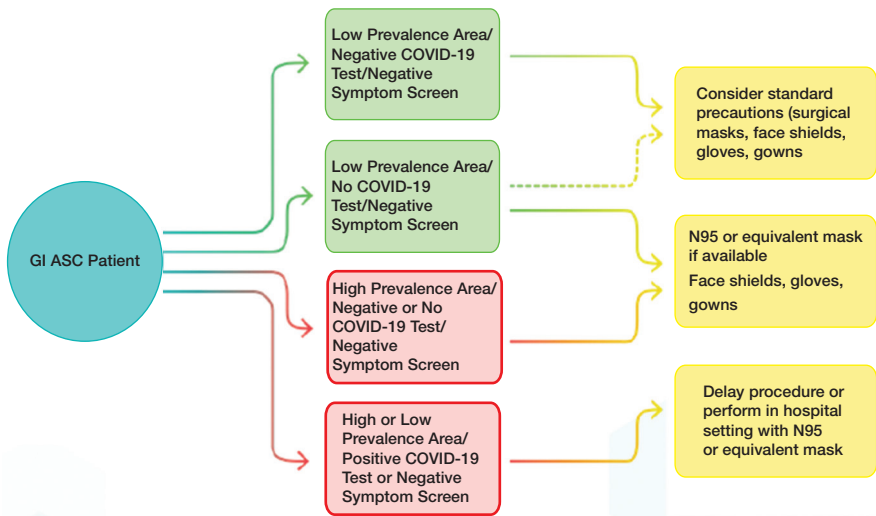
- Use a fitted N95 masks, N99, or powered air-purifying respirators (PAPRs) instead of surgical masks or no masks.
- Double glove instead of single glove.
- If the patient is positive for SARS-CoV2 (or presumptive), use a negative pressure room or, if unavailable in resource-limited settings, use portable industrial-grade high-efficiency particulate air (HEPA) filters in a regular endoscopy room.
- Continue to utilize standard cleaning endoscopic disinfection and reprocessing protocols, which includes mechanical and detergent cleaning using US Food and Drug Administration (FDA)-approved liquid chemical germicide solutions, followed by high-level disinfection (reduces the number of microorganisms by 99.99%), rinsing, and sterile drying. The biocidal agents used in

endoscopic disinfecting solutions have been shown to be effective in inactivating SARS-CoV.<sup>13</sup>

Guidance from the American Society for Gastrointestinal Endoscopy (ASGE) for resuming elective endoscopy as the number of COVID-19 cases decreased includes the following:<sup>14</sup>

- Administer a COVID-19 screening questionnaire to patients within 72 hours prior to the endoscopic procedure to elicit whether the patient had any of the following symptoms within 14 days: fever (100.4 or higher); cough, shortness of breath, difficulty breathing; chest pain; sore throat; loss of sense of smell/taste; new onset of fatigue, nausea, diarrhea, or other significant symptoms. Positive responses should prompt the removal of patients from clinical care areas, (repeat) SARS-CoV2 testing, self-quarantine, and reporting to the proper authorities (eg, Department of Health).
- All members of the endoscopy team should wear N95 respirators (or devices with equivalent or higher filtration rates) for all GI procedures.
- Standard bedside precleaning, followed by manual cleaning and high-level disinfection in the reprocessing facility; no changes are recommended to reprocessing procedures for endoscopes and accessories.

There is flexibility in guidance from the American College of Gastroenterology (ACG) in resuming elective procedures depending on the prevalence of COVID-19, availability of testing, and availability of PPE with N95 or equivalent masks (Figure 8.2). The chart below from the ACG suggests a reasonable algorithm for elective outpatient endoscopic procedure performed in free standing endoscopy centers [15].



**Figure 8.2** Adapted from ACG roadmap for resuming endoscopy.<sup>15</sup>

## 8.4 Liver Diseases

Many patients with COVID-19 either present with liver enzyme abnormalities or develop them over the course of their illness. A meta-analysis showed serum aminotransferase levels--AST or ALT--above the upper limit of normal in roughly 15% of patients and elevated bilirubin in 17%.<sup>16</sup> One study of 1099 patients in China showed that there were more than double the number of patients with an AST >40 with severe illness compared to those with nonsevere illness,<sup>17</sup> and a retrospective study of 1087 patients showed an association between COVID-19 infection and an elevation in baseline liver enzymes, peak liver enzymes, and severity of illness.<sup>18</sup> Of note, there are several confounding factors, such as medications used to treat the infection that were also linked with elevated peak liver enzyme levels.<sup>18</sup>

The mechanism of action of liver injury is unclear but likely secondary to viral infection, inflammatory reaction, or toxin mediated from medications. It is usually transient, but there are case reports of COVID presenting as acute liver injury.<sup>19, 20</sup> Upon autopsy, liver pathology revealed moderate microvesicular steatosis and mild lobular and portal activity.<sup>21</sup> To our knowledge, there have not been reports of fulminant hepatic failure as a result of COVID-19.

An international database has reported 1097 cases of COVID-19 in patients with chronic liver disease at the time of writing of this chapter. The cohort includes 88% hospitalized patients, but does report 18–29% probability of severe disease requiring intensive care admission.<sup>22</sup> Patients with cirrhosis had the worst outcomes with a 32% chance of death. Additional prospective studies will be required to further evaluate the relative and overall risk compared to the general population.

## 8.5 Inflammatory Bowel Disease

Inflammatory bowel disease, namely, Crohn's disease and ulcerative colitis, is estimated to have a prevalence of 6.8 million globally.<sup>23</sup> An international database (SECURE-IBD) has reported 2,156 cases of confirmed COVID-19 in IBD patients from 57 countries (65 deaths, 3%) as of August 31, 2020.<sup>24</sup> The website is available at [covidibd.org](https://covidibd.org) and is continually updated. So far, the use of any of the biologics or Janus kinase (JAK) inhibitor is not associated with higher death rates or worse outcomes.

Patients with IBD are of special consideration during the COVID-19 pandemic as these patients are often treated with chronic immunosuppressive or immune-modifying therapies that include corticosteroids, biologics (including antitumor necrosis factor, anti-integrin, and anti-interleukin therapies), immunomodulators, and 5-aminosalicylic acids.<sup>25</sup> Moreover, patients with IBD may continue to need frequent encounters at health-care facilities for medication administration (infusion of certain biologic therapies), endoscopy (assessment of disease severity in patients with active IBD symptoms), and emergency department visits or hospitalization for IBD flares.

In addition to the recommendations for the general population (social distancing, hand hygiene, work from home, avoid infected persons), IBD patients are recommended

to continue their IBD medication regimens to avoid the risk of relapsing IBD, defer all nonessential endoscopic procedures during surge of COVID-19 cases (including colon cancer screening), and continue to receive medications at infusion centers with appropriate safety protocols (fever checks at the door, chairs spaced at least 6 feet apart, disinfect equipment and furniture after each use, utilize PPE, etc).<sup>25-27</sup>

For IBD patients with GI symptoms, rule out enteric infections, such as *Clostridioides difficile* and other GI pathogens, and test for active inflammation with non-endoscopic approaches, such as biomarkers (serum C-reactive protein, fecal calprotectin), cross-sectional imaging, and capsule endoscopy. During the COVID-19 pandemic, particularly for patients who test positive for SARS-CoV-2, endoscopic procedures should only perform for urgent and emergent indications that “will urgently change management.” This may include scenarios where there is clinical suspicion for a new diagnosis of severe IBD (endoscopy needed for histological confirmation) or stricturing disease causing GI obstruction that need urgent endoscopic decompression, stenting, and evaluation of cancer to guide surgical intervention.<sup>25, 26</sup>

The recommended management of IBD therapies in patients who test positive for SARS-CoV-2 is as follows: continue 5-ASA, budesonide, rectal therapies, and enteral nutrition; hold thiopurines, methotrexate, and tofacitinib; delay 2-week administration of monoclonal biologic therapies; and restart when COVID-19 symptoms resolve or if serological testing demonstrate convalescent stage of the disease.<sup>25</sup> These guidelines will be updated as the SECURE-IBD Registry [24] and other studies provide more data/analysis.

## 8.6 Celiac Disease

A multinational collaboration was created to anonymously report cases of celiac disease and coronavirus.<sup>28</sup> At the time of the writing of this chapter, only 62 cases have been reported, with 82% being treated in the outpatient setting, and 18% inpatient and 2% (1 patient) requiring the intensive care unit (ICU). These data follow the general trend seen with the coronavirus in the general population. In one Italian study, the majority of patients did not feel more vulnerable to the coronavirus given their celiac disease, and half of those surveyed did not worry about the availability of gluten-free food.<sup>29</sup> Overall, it appears that COVID-19 does not impact patients with celiac disease more than the general population.

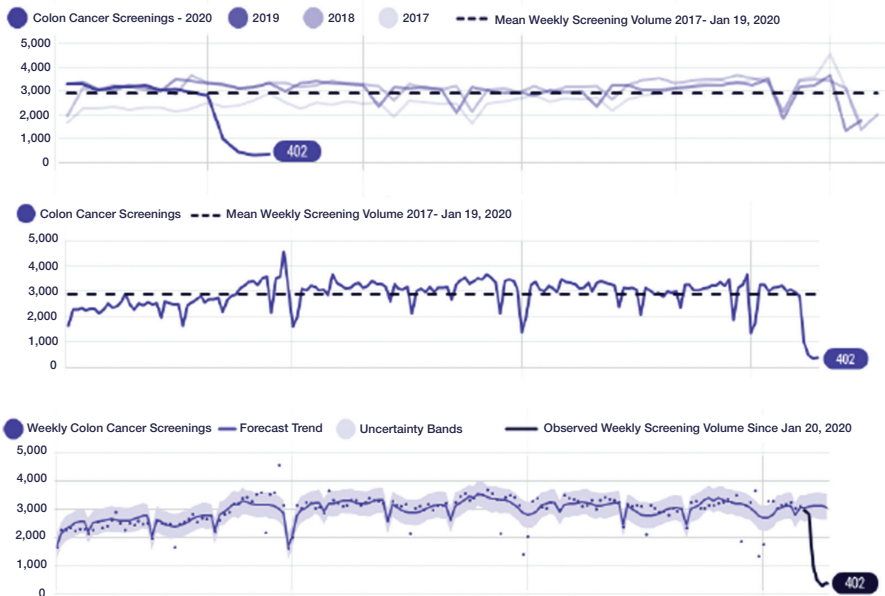
## 8.7 GI Cancers

In general, patients with comorbidities, including cancer of all types, have a higher risk for severe COVID-19.<sup>30</sup> As such, various oncological and GI professional societies have produced guidelines for which procedures, therapies, and screenings are appropriate.

Currently, there is no evidence which necessitates withholding systemic chemotherapy or immunotherapy for cancer.<sup>31</sup> However, the Infectious Disease Society of America recommends that patients receiving cytotoxic chemotherapy should be

tested for SARS-CoV-2 RNA even if asymptomatic.<sup>32</sup> According to the Society of Surgical Oncology, in gastric and esophageal cancers, staging laparoscopy may be skipped in favor of beginning neoadjuvant therapy directly in a COVID-19-positive patient, in order to reduce transmission risk and use of PPE. Patients on neoadjuvant therapy for gastric and esophageal cancers may also continue chemotherapy if they are responding to treatment and there is not enough PPE to proceed with surgical resection. Physicians at Sloan Kettering have deemed resection of colon, stomach, pancreas, and liver cancers as “essential,” as patient outcomes will be worsened with delay.<sup>33</sup> This approach was also validated by guidance from the American College of Surgeons (ACS) and the New York State Department of Health. Full guidelines provided by Oncological and Gastrointestinal Societies are provided in the “Cancer Screening Guidelines” section. On the other hand, others advocate that chemotherapy may also be used to delay surgery for hepato-pancreato-biliary cancer, as long as the patient is responding to and tolerating treatment.<sup>34</sup>

Cancer screening guidelines have also been changed due to COVID-19. The American College of Physicians recommends a colonoscopy every 10 years or a sigmoidoscopy every 5 years between 50 and 75 years of age.<sup>35</sup> However, due to the pandemic, these important screenings are being delayed. A study gathered from the EPIC electronic health records system involving 2.7 million patients across 39 health systems with 190 hospitals and spanning 23 states in the USA demonstrated screening appointments for breast, colon, and prostate cancer in March of 2020 decreased by 86% compared to mean volumes from January 1, 2017, to January 19, 2020 (Figure 8.3).<sup>36</sup> The graphs of the drop in colon cancer screening are featured



**Figure 8.3** Screening appointments for cancers between 2017 and March 2020.<sup>36</sup>

below. The charity Cancer Research UK estimates a backlog of 2.1 million patients waiting for breast, colon, or cervical cancer screening. Normally, about 3800 cancers would be diagnosed over this time period.<sup>37</sup> In Hong Kong, screening endoscopies and colonoscopies reached a turning point and began to decrease in January 2020. The mean weekly numbers of gastric and colon cancer diagnoses decreased by 46 and 37%, respectively.

- Cancer Research UK’s Dr. Charles Swanton warns that “delays to diagnosis and treatment could mean that some cancers will become inoperable” [37]. While the European Society for Gastrointestinal Endoscopy Guidelines (ESGE) and other GI professional societies recommend noninvasive procedures such as the fecal immunohistochemistry (FIT) test in the meantime, there cannot be an indefinite delay—there is a significant increase in cancer risk with a >6-month delay in colonoscopy after positive FIT test.<sup>35</sup> Already the effects of decreased screening are becoming apparent. As a result of the NHS suspending cancer screening, 3800 people in the UK whose cancer would have been picked up by screening have gone undiagnosed and another 20,300 cancers may also have been missed due to an estimated 290,000 patients with symptoms of possible cancer who were not urgently referred for evaluation.<sup>30</sup> Statistical models of data from Hong Kong show that 4.6% of gastric cancers and 6.4% of colon cancers would have a more advanced stage of cancer at detection 6 months after the decrease in screenings.<sup>37</sup> The data from these studies from Hong Kong, the UK, and the United States demonstrate the danger of prolonged deferment of screening—many treatable cancers (not just colorectal cancer) will progress unnoticed until it may be too late for the patient. Gradually resuming elective endoscopic procedures may begin to mitigate some of these effects for colon cancer.<sup>38</sup> Tracking patients whose elective procedures have been delayed and getting them rescheduled is an important part of this process. As such, it is of utmost importance for hospitals and endoscopy centers to safely resume screening endoscopies and colonoscopies, before there is a major increase in preventable GI cancers.

#### GI Cancer Treatment Guidelines:

- <https://www.facs.org/covid-19/clinical-guidance/elective-case/colorectal-cancer>
- <https://www.surgonc.org/resources/covid-19-resources/>
- <https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic>
- <https://www.futuremedicine.com/doi/10.2217/crc-2020-0010>
- Modifying Practices in GI Oncology in the Face of COVID-19: Recommendations From Expert Oncologists’ Recommendations on Minimizing Patient Risk (<https://www.nccn.org/covid-19/pdf/Colorectal%20COVID-19.pdf>)

## 8.8 Telehealth in GI

Telehealth in GI is an important tool to allow patients to access care without interruption during the COVID-19 pandemic. Though only a minority of gastroenterologists (private or academic) were offering telehealth services prior to COVID-19, the vast majority have rapidly adapted this technology for offering care and will likely continue this option as patients find it convenient and cost/time-effective. Most electronic health platforms have incorporated a telehealth option, and there are several inexpensive or free platforms such as [Doxy.me](#) or Doximity. This access to care is particularly important in optimally managing chronic conditions, including IBD and liver disease. The American Gastroenterological Association (AGA) and the American College of Gastroenterology (ACG) assisted GI practices with their transition to telehealth by partnering the following:

- Rx Health: a Virtual Care Hub and Telehealth platform for digital screening and triaging of patients before in-person appointments, accommodate virtual visits through a dedicated telehealth room, and patient access to GI education modules from the AGA patient education center.
- GI OnDEMAND, a Health Insurance Portability and Accountability Act (HIPAA)-compliant and cloud-based telehealth system where providers can get reimbursed for out-of-office patient support and patients can access an online support community and evidence-based health information.

For information on billing and coding of telehealth visits, please refer to the following resources:

- HHS FAQs on telehealth and HIPAA: <https://www.hhs.gov/sites/default/files/telehealth-faqs-508.pdf>
- AMA 2021 E/M codes and guidelines: <https://www.ama-assn.org/system/files/2019-06/cpt-office-prolonged-svs-code-changes.pdf>

## 8.9 Proton Pump Inhibitors and COVID-19

Proton pump inhibitors (PPIs) suppress the production of gastric acid contents and are commonly used to treat esophageal and gastric diseases such as GERD, esophagitis, Barrett's esophagus, and peptic ulcer disease. There is conflicting data regarding an association or causation between PPI and COVID-19 infection rate as well as severity. One large survey-based study of more than 50,000 patients in the United States showed a dose-responsive relationship between PPIs and COVID infection; however, a larger retrospective study in Korea did not find any significant difference in infection rate between PPI users and nonusers.<sup>39, 40</sup> The latter study did find that PPI use correlated with a more severe course of illness. To date, no randomized control trials have been published regarding PPI use and development of COVID-19.



Studies on SARS-CoV-1 suggested the virus was less infective at lower pH, providing a potential mechanism for increased infectivity.<sup>41</sup> Interestingly, with regard to the current studies on SARS-CoV-2, there was no similar association between SARS-CoV-2 and histamine-2 blocker use, which also lowers gastric pH, indicating that there may be other pathophysiologic mechanisms to infection. Famotidine was actually associated with a decreased risk of intubation or death, and is currently being investigated as a potential treatment for the virus.<sup>42, 43</sup>

An association between PPIs and COVID-19 is concerning, particularly given the prevalence of PPI use in modern society; however, it needs to be further evaluated with prospective studies and randomized controlled trials to determine causation. Until these studies are completed, we recommend that practitioners discuss this data with patients, using shared decision-making to determine whether to continue with PPIs or consider a transition to alternate therapies, such as H-2 blockers. The American Journal of Gastroenterology has also published an information sheet noting that the absolute risk of COVID-19 infection is low and that social distancing and masks will have a much greater impact on personal risk of acquiring COVID-19 than adjusting PPI dosing.<sup>44</sup> As we await further trials, for now it is prudent to consider the potential increased risk for COVID-19 when discussing the use of PPIs with patients.

## 8.10 Tools for Health-care Providers

- American College of Gastroenterology—COVID and GI: <https://gi.org/media/covid-19-and-gi/>
- AASLD COVID-19 resources <https://www.aasld.org/sites/default/files/2020-06/AASLD-COVID19-ExpertPanelConsensusStatement-June42020-FINAL.pdf> ACG COVID-19 resources: <https://gi.org/media/covid-19-and-gi/>
- AGA COVID-19 resources: <https://www.gastro.org/practice-guidance/practice-updates/covid-19>
- ASGE COVID-19 resources: <https://www.asge.org/home/advanced-education-training/covid-19-asge-updates-for-members/>
- Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) <https://covidibd.org/>

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# Renal Manifestations of COVID-19

## CHAPTER 09

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### List of Abbreviations

ACE-2	Angiotensin-converting enzyme-2
ACEIs	Angiotensin-converting enzyme inhibitors
AKI	Acute kidney injury
ANP	Atrial natriuretic peptide
ARBs	Angiotensin receptor blockers
ARDS	Acute respiratory distress syndrome
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
CVP	Central venous pressure
GFR	Glomerular filtration rate
KDIGO	Kidney Disease Improving Global Guidelines
ICU	Intensive care unit
MAP	Mean arterial pressure
PEEP	Positive end-expiratory pressure
RRT	Renal replacement therapy
VTE	Venous thromboembolism

### 9.1 Introduction

Acute kidney injury (AKI) is a major health concern as it often results in fatal complications following intensive care unit (ICU) admission. COVID-19 is a peculiar disease with a highly variable disease course, and it has been seen to have multiple renal manifestations. These can range from symptoms like hematuria to the development of acute kidney failure. The rapidly progressive kidney damage warrants early admission and a close clinical monitoring.

Multiple mechanisms leading to the development of renal manifestations have been proposed, including volume depletion effects, systemic inflammation, hemodynamic disturbances, direct viral invasion, and rhabdomyolysis, among others.

While maintenance of adequate fluid balance is pivotal, parameters such as oxygen saturation, blood urea nitrogen (BUN), creatinine, urine output, and arterial or venous pressures should be closely monitored. Early assessment of volume status through the combined use of physical examination and ultrasound imaging is essential to avoid renal complications. Maintenance of euvolemia using appropriate hydration, fluid-reducing medications, and other necessary measures is the single most important step.

Another more worrisome complication is the development of venous thromboembolism (VTE) in some patients. Heparin prophylaxis or other anticoagulation may be used in the hospital setting to prevent VTE in COVID-19 patients. Use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in COVID-19 patients is controversial due to the possibility of worsening of the disease course. Thus, we advise that clinicians exercise extreme precaution while using any of these medications.

## 9.2 Epidemiology

There is mounting evidence that COVID-19 can manifest as AKI. Though the pool of data collected on this subject is preliminary, it is clear that there is a trend of renal injury beyond simply the baseline level expected in similar populations. A recent study of 193 COVID-19 patients in Wuhan, China, reported that many patients showed signs of kidney dysfunction upon admission to the hospital. More than half of these patients had proteinuria, about half had hematuria, and some had increased BUN and creatinine levels.<sup>1</sup> The multinational Acute Kidney Injury-Epidemiologic Prospective Investigation (AKI-EPI) study estimated the baseline level of AKI incidence in all ICU admissions to be 57.3%, while 13.5% of all ICU admissions develop severe AKI requiring renal replacement therapy (RRT).<sup>2</sup> This latter number is known to be higher in cases of acute respiratory distress syndrome (ARDS). The American Society of Nephrology estimates from many preliminary studies that the incidence of AKI in COVID-19 admissions is likely similar to the baseline, but the percentage of COVID-19 ICU cases with severe AKI requiring RRT is increasing at an upward rate of 30%.<sup>3</sup>

Thus, the current research suggests that COVID-19 patients often end up with much more severe kidney injury. This is important as AKI can increase an already high mortality risk in these patients. A univariate Cox regression analysis showed that proteinuria; hematuria; and increased BUN, serum creatinine, and uric acid levels were all significantly associated with death in COVID-19 patients. This study also found that COVID-19 patients who developed AKI had an increased mortality risk compared to those without AKI by a factor of 5.3.<sup>1</sup>

Given the propensity of COVID-19 to damage the kidney, it poses an even greater danger to patients who already carry a diagnosis of chronic kidney disease (CKD). A recent meta-analysis preprint reported that patients with CKD have a six-fold increased risk of developing severe COVID-19 infection over the general population.<sup>4</sup>

### 9.3 Pathophysiology of COVID-19 Renal Manifestations

There have been multiple suggested etiologies of AKI due to COVID-19.<sup>3</sup> These etiologies likely work together to attack the kidney from several angles. These can be broadly categorized in the following.

**Fluid Balance:** Aggressive diuresis is often necessary in the management of COVID-19 patients. This can lead to hypovolemia, causing the body to decrease the glomerular filtration rate (GFR) to preserve fluid.

**ARDS Side Effects:** The lung is one of the main sites of interest for the virus due to the abundance of ACE2 receptors on pneumocytes. The inflammatory process in the lung results in an increased cytokine activity throughout the body. Furthermore, this can lead to increases in neurohormonal pathway activation in the sympathetic nervous system and the renin–angiotensin–aldosterone system, while causing decreases in atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels. Altogether, these effects have a harmful effect on GFR and cause inflammatory damage to renal vessels and parenchyma.

**Hemodynamic:** The use of high positive end-expiratory pressure (PEEP) in patients on ventilators can increase pressure in the thoracic cavity. This can cause low-pressure venous vessels with large blood-carrying capacity to collapse under the pressure. With less available volume in the thoracic venous vessels, such as the superior and inferior vena cava, venous blood will back up and cause congestion in multiple organs, including the kidney. Furthermore, the lower venous return to the heart will lead to decreased preload and cardiac output, hence reducing the pressure in the renal arteries. These two hemodynamic functions together cause a decrease in renal glomerular filtration pressure and can reduce GFR.

**Hypoxemia and Hypercapnia:** The inability to properly oxygenate blood and offload carbon dioxide in the lungs can lead to chemical and acid–base anomalies, which are harmful to the renal regulatory systems. Hypoxemia on its own can reduce renal blood flow. Carbon dioxide retention acidifies the blood, forcing the kidney to work harder to reabsorb bicarbonate and maintain physiologic pH. This in turn increases the oxygen demand in the kidney. Thus, the kidney becomes particularly susceptible to hypoxic damage. In addition, hypercapnia has been known to cause a decrease in the renal autoregulatory system that maintains GFR and protects the kidney from hydrostatic pressure damage.

**Rhabdomyolysis:** While not common, there have been case reports and a few studies that have reported increases in myoglobin and creatine kinase levels in the blood of COVID-19 patients.

**Direct Viral Infection:** Though unclear, it has been suggested that the virus can directly infect the renal parenchyma. This may be due to renal expression of the ACE2 surface protein, which acts as a coreceptor for the viral entry of COVID-19 into the cell.

As can be seen, there are multiple possible etiologies for renal damage and AKI due to infection with COVID-19. There is evidence to support each of these etiologies, so it is likely that they work in conjunction to unleash a multifaceted attack on the kidney.<sup>3</sup>

## 9.4 Monitoring COVID-19 Patients for AKI

Due to the numerous possible ways that the kidney can be damaged from this virus, it is important to keep a watchful eye on many parameters for patients with this diagnosis. Recognizing AKI in COVID-19 is no different from recognizing it in other situations; the American Society of Nephrology recommends using the well-known KDIGO (Kidney Disease Improving Global) Guidelines.<sup>5</sup> This involves consistently monitoring parameters such as BUN, serum creatinine, and urine output.<sup>3</sup>

Beyond these direct parameters, it is also important to monitor multiple values that may indicate an impending AKI.<sup>3</sup> As there are many different possible etiologies of AKI as was explained earlier, the parameters to monitor can be broken down by each etiology.

**Fluid Balance:** It is recommended to assess the true volume status of each patient. This should involve a multifaceted approach involving physical examination, passive leg raise test, pulse wave analysis, point-of-care ultrasound, and electrolyte levels. Simply estimating the volume status from a few parameters can lead to false assessments of the fluid balance. Efforts should be made to maintain the patient at euvolemia with normal electrolytes for best renal protection.

**ARDS Side Effects:** High levels of cytokines and neurohormonal activity can cause damage to renal structure and function. Thus, it is important to monitor inflammatory markers and BNP to ensure early detection of abnormalities and swift response by the appropriate medical teams.

**Hemodynamic:** As explained previously, the hemodynamic effects of COVID-19 and its management can have deleterious effects on renal function. It is therefore important to estimate or calculate the central venous pressure (CVP), mean arterial pressure (MAP), cardiac output, and renal perfusion pressure. Without appropriate pressure in the renal vessels, the kidneys will not be able to maintain the necessary GFR. Calculating the volume status of the patient will also play a key role in understanding the hemodynamic status in this patient. Furthermore, patients on ventilators should be monitored for appropriate PEEP, tidal volume, and peak inspiratory pressures. Concerns regarding these settings should be discussed with the appropriate teams to ensure the safest balance of ventilation and hemodynamics.

**Hypoxemia and Hypercapnia:** The blood oxygen saturation is important to monitor in COVID-19 patients not only for the integrity of the lungs, but also

for the kidneys. Beyond just the saturation, imbalance in oxygen and carbon dioxide levels can have many serious effects on kidney function, so it is important to monitor parameters such as the arterial blood gases and the arterial pH to assess the acid–base status and gas-exchange function of the patient.

**Rhabdomyolysis:** Though this is a less common direct etiology of renal damage, the medical team can consider monitoring myoglobin and creatine kinase levels, especially when there is a high suspicion of rhabdomyolysis.

**Direct Viral Infection:** Evidence of direct viral infection of the kidney can occasionally be found on biopsy with immunofluorescence, but this is not recommended as a monitoring strategy.

As can be seen, the list of important parameters to monitor is quite vast. A summary of these parameters, as well as the corresponding pathophysiological importance, is given in Table 9.1. Fortunately, some of these parameters can be measured noninvasively, while many of the invasive tests may provide an expanded value due to their importance to other organ systems beyond the kidney. While it may be especially difficult to find sufficient time to fully assess the patients regularly due to high patient load in a pandemic setting, every effort should be made by all responsible teams to keep these etiologies in mind when considering each patient.<sup>3</sup>

## 9.5 Early Management of AKI

While suspicion of kidney injury should prompt a discussion with a nephrology team, it is important for all medical parties to understand the basic early management of AKI. The early management heavily depends on the adequate assessment of volume status, as discussed earlier. A combined approach using physical examination (including assessment of edema, weight changes, and capillary refill), passive leg raise test, pulse wave analysis, and point-of-care ultrasound is essential for assessing the true volume status beyond simple estimation from few parameters, which is prone to error. Once this is established, the initial management goal should be to ensure that the patient is euvolemic. Some evidence suggests the use of furosemide stress test to predict the progression of AKI. However, the evidence is limited and requires further study.<sup>3</sup>

It is important to stress here that the use, or lack thereof, of fluid-reducing medications is vital for multiple organ systems in COVID-19 patients. Therefore, it is important that all teams responsible for the patient come to an understanding of what steps be taken in managing the patients prior to adding or removing medications. However, any member of the care team can carry out an assessment of the volume status, which is a crucial step in deciding management. Thus, the primary team should initially focus on assessing this in order to facilitate the conversations between the multiple responsible medical teams.



**Table 9.1** Etiologies of Kidney Damage in COVID-19 Patients, with Summarized Pathophysiology and Management Strategies

Etiology	Pathophysiology	Monitoring Recommendation
Fluid balance	Aggressive diuresis during hospital management can cause iatrogenic hypovolemia	<ul style="list-style-type: none"> <li>Assess true volume status with physical examination, passive leg raise test, pulse wave analysis, point-of-care ultrasound, and electrolyte levels</li> <li>Maintain patient at euvolemia with normal electrolyte ranges</li> </ul>
ARDS side effects	Inflammation in the lung causes increased cytokine activity and activates the sympathetic nervous system and the renin–angiotensin–aldosterone system, while decreasing ANP and BNP	<ul style="list-style-type: none"> <li>Monitor inflammatory markers and BNP</li> </ul>
Hemodynamics	High PEEP causes decreased venous return. This leads to backup of blood flow in the kidneys as well as lower perfusion due to decreased preload and cardiac output	<ul style="list-style-type: none"> <li>Estimate or calculate CVP, MAP, cardiac output, and renal perfusion pressure</li> <li>Carefully monitor PEEP, tidal volume, and peak inspiratory pressures</li> <li>Maintain good communication with all teams responsible for ventilator adjustments</li> </ul>
Hypoxemia and hypercapnia	Decreased lung function causes hypoxemia, hypercapnia, and respiratory acidosis. This has harmful effects on the renal regulatory system, and it increases the energy demand of the kidney as it works to compensate for the acidosis	<ul style="list-style-type: none"> <li>Assess acid–base status and gas-exchange function with arterial blood gas, pH, and oxygen saturation</li> </ul>
Rhabdomyolysis	COVID-19 patients have been reported to have increased serum myoglobin and creatine kinase levels	<ul style="list-style-type: none"> <li>Consider monitoring myoglobin and creatine kinase levels, especially if there is high suspicion of rhabdomyolysis</li> </ul>
Direct viral infection	Renal expression of ACE2 makes it theoretically possible for the virus to directly attack the kidney, though this has not been fully studied	<ul style="list-style-type: none"> <li>No current monitoring recommendations</li> </ul>

## 9.6 Note on Venous Thromboembolism (VTE) and Prophylaxis

One of the concerns raised in COVID-19 patients was the presence of VTE that proved fatal. However, the evidence for this seems to be mainly from case studies and preliminary observational trials rather than robust, large-scale studies. A single-center cohort study from the University of Amsterdam was conducted with 198 hospitalized COVID patients, 75 of which were admitted to the ICU. The 21-day cumulative incidence of VTE was 42%. The 21-day cumulative incidence of VTE was higher in the ICU (59%) compared to the wards (9.2%).<sup>6</sup> These results add to the growing pool of evidence associating COVID-19 infection with VTE, and different health-care institutions have responded to this by devising their own protocols to provide adequate VTE prophylaxis to the patients. Some of these protocols are based on D-dimers and require the administration of heparin as a part of their prophylaxis guidelines. Thus, it is important to consider anticoagulation in COVID-19 patients, and the monitoring and administration practices should be deferred to hospital protocols and case-by-case analysis.<sup>3</sup>

A study in Tongji Hospital in Wuhan, China, retrospectively analyzed the 28-day mortality between heparin and nonheparin users among severe COVID-19 patients. It was concluded that anticoagulation with low molecular weight heparin was associated with a better prognosis in patients who met the sepsis-induced coagulopathy criteria with increased levels of D dimers.<sup>7</sup> This study can be considered when devising an appropriate protocol for anticoagulation.

## 9.7 Note on ACE Inhibitor and ARB Usage in COVID-19

The use of medications such as ACEIs and ARBs has been shown in some animal trials to increase the expression of the ACE2 receptor. Given that the COVID-19 virus uses ACE2 as a coreceptor to enter the cells, there is a concern that the use of these medications may increase susceptibility to the infection. ACE2 is present in various body viscera such as kidneys, heart, gastrointestinal system, and type II alveolar cells in the lungs.<sup>8</sup> The role of ACE2 in the healthy body is to convert angiotensin II into angiotensin (1–7), which has a vasodilatory effect that is protective in various lung injury models. Evidence suggests that angiotensin (1–7) prevents oxidative stress and also plays a role in controlling inflammation and fibrosis in the renal tissues and beyond. In a trial involving rats, it was found that angiotensin (1–7) modulates the vascular responses to vasoconstrictors and prevents nitric oxide-induced oxidative stress.<sup>9</sup> Thus, it is currently unknown whether ACE inhibitors or ARBs are beneficial or harmful during COVID-19 infection. The current recommendation is for patients taking ACE inhibitors or ARBs to continue their regimen. However, the Randomized Elimination or ProLongation of Angiotensin Converting Enzyme inhibitors and angiotensin receptor blockers in Coronavirus Disease 2019 (REPLACE COVID) trial is currently underway at the University of Pennsylvania, which will investigate the effects of temporarily stopping these medications in patients hospitalized with COVID-19.<sup>10</sup>

## 9.8 Conclusion

- The development of AKI in COVID-19 patients increases the risk of mortality.
- Monitoring kidney function should be monitored with BUN, creatinine, and urine output.
- Assessment of volume status and maintenance of euvolemia is an essential management step. Fluid-reducing medicines should be used with caution to avoid AKI.
- Measuring inflammatory markers and BNP can assess the level of systemic inflammation.
- Adequate VTE prophylaxis either using heparin or using other anticoagulating agent should be considered for hospitalized patients.
- ACEIs and ARBs should be used with care as the efficacy of these medicines in COVID-19 patients is poorly understood.
- RRT is recommended for patients who can no longer be managed on medications.

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# Endocrine Manifestations of COVID-19

## CHAPTER 10

Sudhir Bansal M.D. and Farhan Qureshi

### List of Abbreviations

ACE2	Angiotensin-converting enzyme 2
ACTH	Adrenocorticotrophic hormone
ARB	Angiotensin receptor blocker
CRP	C-reactive protein
DKA	Diabetic ketoacidosis
DPP4	Dipeptidyl peptidase 4
ESR	Erythrocyte sedimentation rate
GLP-1	Glucagon-like peptide-1
HPA	Hypothalamic–pituitary–adrenal
MERS-CoV	Middle East respiratory syndrome coronavirus
SARS-CoV-1	Severe acute respiratory syndrome coronavirus
SGLT-2	Sodium/glucose cotransporter-2
T2D	Type 2 diabetes

### 10.1 Overview

Worldwide, over 400 million are affected by diabetes, with over 1.6 million deaths attributable to diabetes alone in 2016.<sup>1</sup> In the United States in 2018, 10.5% of the population had diabetes, which is the seventh leading cause of death.<sup>2</sup> Diabetes is a multiorgan disease and leads to worse outcomes in many other diseases when it is a comorbid condition. Previous viral outbreaks have shown us that diabetes is a very important risk factor to consider. Diabetes was associated with poor outcomes during the severe acute respiratory syndrome coronavirus (SARS-CoV-1) outbreak in the early 2000s<sup>3</sup> and the H1N1 outbreak in 2009, and was associated with more severe infection and a higher mortality rate during the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012.<sup>4</sup>

Currently, diabetes is the third most common comorbidity in COVID-19 patients,<sup>5</sup> is associated with more severe disease,<sup>6</sup> and increases patients' risk of ICU

admission.<sup>7,8</sup> Most notable, however, are diabetes and obesity that are both independently associated with a higher risk of death in COVID-19 patients.<sup>8</sup> In light of these data, and by understanding the data from previous viral outbreaks, it is imperative to understand the interaction between this viral pandemic and the global epidemic of diabetes.

## 10.2 Mechanisms of Increased COVID-19 Severity in Diabetic Patients

In general, diabetic patients are more susceptible to infection due to dysfunctional immune responses such as decreased neutrophil chemotaxis and decreased phagocytosis by the innate immune cells.<sup>9-11</sup> Immune cell function, like killing via respiratory burst, is also inhibited by hyperglycemia seen in diabetic patients.<sup>11</sup> Diabetic patients have decreased proportions of CD4+, CD8+, and anti-inflammatory regulatory T cells, and also have a higher proportion of pro-inflammatory immune cells (eg, Th17 cells).<sup>11</sup> This altered immune landscape may allow inflammatory cascades to go unchecked in diabetic patients. There is also evidence that patients with hypertension and diabetes have a delayed clearance of viral load, prolonging infections.<sup>10</sup> With respect to SARS-CoV-2 specifically, it is theorized that diabetes increases the risk of infection due to up-regulation of angiotensin-converting enzyme 2 (ACE2), which the virus uses to infect cells.<sup>9,10</sup>

The effects of diabetes on ACE2 are twofold. While acute hyperglycemia has been shown to up-regulate ACE2, there is evidence that chronic hyperglycemia down-regulates ACE2 expression. This effect of ACE2 down-regulation may, however, increase the inflammatory damage caused by COVID-19, as ACE2 is protective against inflammation.<sup>9</sup> Diabetic patients also have increased levels of plasmin and plasminogen, and protease enzymes thought to play a role in SARS-CoV-2 infectivity. Plasmin(ogen) cleaves furin sites in SARS-CoV-2 S proteins, which increases infectivity by allowing easier entry, fusion, duplication, and release of viral particles in respiratory cells. Elevated plasmin(ogen) and furin levels are common in COVID-19 diabetes and may also be an independent factor for risk stratification.<sup>11</sup> Another way diabetes exacerbates COVID-19 symptoms is its effects on the respiratory system. Diabetes can cause altered lung capillary permeability and small airway collapse. Additionally, SARS-CoV-2 can decrease the O<sub>2</sub>-carrying capacity of hemoglobin, which is exacerbated in the glycated hemoglobin in diabetic patients.<sup>11</sup>

Not only does diabetes exacerbate the symptoms of COVID-19, COVID-19 also exacerbates the symptoms of diabetes. A study of 658 patients in Wuhan, China, showed that 6.4% presented with ketosis, and these patients had worse outcomes and longer hospital stays. In a smaller proportion of patients, this ketosis precipitated into diabetic ketoacidosis (DKA), which is a serious complication of diabetes. Interestingly, of the five total DKA cases, two of the patients were nondiabetic.<sup>12</sup> A

case study in Singapore also showed DKA precipitated by COVID-19.<sup>13</sup> The mechanism of COVID-19-induced DKA is unclear; however, it is postulated that direct damage to pancreatic beta cells due to infection causes an acute insulin deficiency that can precipitate DKA.<sup>9, 13</sup>

### 10.3 Managing Diabetes in COVID Patients

Management of glycemia is of utmost importance in COVID-19 patients. Data from an Italian study shows that diabetic patients with hyperglycemia are at a higher risk of developing severe COVID-19 and have persistently higher levels of inflammation (measured by IL-6 and D-dimer), than diabetic patients who are normoglycemic. Data from a retrospective study in Hubei Province, China, shows that maintenance of glycemia within 3.9–10 mmol/L in patients with preexisting type 2 diabetes (T2D) is associated with a significant reduction in morbidity and mortality.<sup>14</sup>

Glycemia in T2D patients may be managed by a plethora of medications, which may have implications for SARS-CoV-2 infection. Because ACE2 is important for viral entry into cells, upregulation of ACE2 may be detrimental. Several classes of diabetes medications may be implicated in this: sodium/glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor antagonists, pioglitazones, and possibly insulin.<sup>15</sup> Most notable, however, are the ACE inhibitors and angiotensin receptor blockers (ARB). Preclinical models indicate that ACE2 may be up-regulated by ACE inhibitors/ARBs, raising concerns for their use in COVID-19 patients. However, new clinical data indicates that their use is safe and effective in COVID-19 patients.<sup>16</sup> An additional consideration when choosing medications is the involvement of inflammation in the COVID-19 disease process. Dipeptidyl peptidase 4 (DPP4), which is involved in inflammatory pathways, is the target of incretin-based therapies used for T2D. Preclinical studies show a decreased inflammation with DPP4 inhibition, and similar effects are seen with SGLT-2 inhibitors and pioglitazone,<sup>15</sup> raising the question whether these therapies would be more appropriate for use in diabetic COVID patients.

It must be noted that currently, there have been no changes in guidelines for managing diabetes in COVID-19 patients. Furthermore, there is no evidence of poor outcomes when treating diabetic patients with any of the abovementioned medications,<sup>17</sup> which are summarized in Table 10.1 (adapted from Pal et al., 2020). In the inpatient setting, insulin infusion may be the best method for achieving glycemic targets and improving outcomes due to its safety and reliability.<sup>18</sup> However, other factors must be considered when treating an infectious disease—namely, reduction of contact with COVID-positive patients. Therefore, physicians must choose a regimen that fits their primary target (glycemic control vs. contact frequency). For instance, if the physician wishes to reduce contact, they may use an NPH-regular regimen.<sup>19</sup> Such pros and cons are listed in Table 10.2 (adapted from Hamdy et al.<sup>19</sup>).

**Table 10.1** Commonly Prescribed Antidiabetic Drugs and Concerns Regarding Their Use during COVID-19

Antidiabetic Drug	Data from Animal Studies	Data from Human Studies	Concerns for Use during COVID-19 Pandemic
Insulin	Reduces renal ADAM-17 expression in diabetic mice, thereby reducing urinary ACE2 shedding and increasing intrarenal ACE2 expression	–	No human data to support poor outcome
Metformin	–	–	No concern
Sulfonylureas	–	–	No concern
Pioglitazone	Up-regulation of ACE2 in insulin-sensitive tissues of rats	Down-regulation of ADAM-17 in human skeletal muscles	Theoretical risk of poor outcome; however, no data on human pulmonary ACE2 expression
Liraglutide	Up-regulates ACE2 in cardiac and pulmonary tissues of diabetic rats	–	Theoretical risk of poor outcome; however, no data on human pulmonary ACE2 expression
SGLT2 inhibitors	–	Promotion of renal ACE2 activity	Theoretical risk of poor outcome; however, no data on human pulmonary ACE2 expression
DPP4 inhibitors	DPP4 mice develops severe disease with MERS-CoV DPP4i; ACE2 activity is not altered in diabetic mice	DPP4 inhibitor might exert overall anti-inflammatory role	Theoretically, DPP4 modulation might help offset the cytokine-mediated acute respiratory complications of COVID-19
Hydroxychloroquine	–	Reduction of viral load in COVID-19	Can be considered as a third-line add-on drug in patients with poor glycemic control

Abbreviations: COVID-19, coronavirus disease 2019; ACE2, angiotensin-converting enzyme 2; ADAM-17, a disintegrin and metalloproteinase-17; SGLT-2, sodium/glucose transporter 2; DPP4, dipeptidyl peptidase 4; DPP4, transgenic diabetic mice expressing human DPP4; MERS-CoV, Middle East respiratory syndrome coronavirus.

**Table 10.2** Pros and Cons of Several Insulin Regimens Used in the ICU for Patients with Diabetes and COVID-19 on Continuous Tube Feeding

	Insulin Infusion, i.v.	Basal Insulin q12h + Regular Insulin q6h for Correction	NPH insulin q8h + Regular Insulin q8h for Correction	Regular Insulin q6h
Contact frequency/day	24	4	3	4
Glycemic control	++++ (best)	+++	++	+
Glycemic variability	+ (lowest)	++	+++	++++
Risk of hypoglycemia upon TF interruption	–	++++	+++	++
Mitigation protocol	Relax the target blood glucose and test q2-4h	Reduce doses of basal insulin and add fixed doses of regular insulin q6hr plus correction by regular insulin q6h	No mitigation is required	No mitigation is required
			Infuse D10W at the same rate if TF is interrupted for >2h	
		Infuse D10W at the same rate if TF is interrupted for >2h		

Abbreviations: D10W, dextrose 10% in water; TF, continuous tube feeding.

## 10.4 Other Endocrine Diseases

### 10.4.1 Adrenal Insufficiency

SARS-CoV (coronavirus which caused the 2003 SARS epidemic) employs an immunoevasive technique wherein it knocks down the host cortisol stress response. It does so by mimicking amino acid sequences of host adrenocorticotrophic hormone (ACTH). Because SARS-CoV-2 is related to SARS-CoV, it is theorized that COVID-19 may affect the hypothalamic–pituitary–adrenal (HPA) axis. There are currently prospective studies underway to analyze this.<sup>20</sup>



Independently of COVID-19's effects on the HPA axis, glucocorticoids have been employed to treat the cytokine storm, which causes many of COVID-19's worst symptoms. Those with adrenal insufficiency should be treated with double the dose of glucocorticoids, according to the American Association of Clinical Endocrinologists.<sup>20, 21</sup> For patients with adrenal insufficiency and COVID-19 presenting persistent fever or severe pneumonias, the preferred treatment is an initial bolus of 50–100 mg hydrocortisone followed by a continuous IV replacement. This regimen reduces the immunosuppressive effects of high peaks of hydrocortisone and has been shown to reduce time in the ICU.<sup>21, 22</sup>

#### 10.4.2 Subacute Thyroiditis

Subacute thyroiditis is an inflammatory thyroid disease, which is generally precipitated by a viral infection of the upper respiratory tract. The first reported case of subacute thyroiditis after SARS-CoV-2 infection has been confirmed in Italy. Fifteen days after testing positive for SARS-CoV-2 via oropharyngeal swab, the patient presented with tachycardia and an inflamed and painful thyroid. FT4 and FT3 were high in this patient, with an undetectable TSH, and negative TPOAb and TRAb. High FT4 and FT3 indicate hyperthyroidism, while negative thyroid antibodies indicate a non-autoimmune etiology. Inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were high along with white blood cell count. After treatment with prednisone for over one month, the symptoms resolved and both inflammatory markers and thyroid tests were normal.<sup>23</sup> This case represents another clinical manifestation of COVID-19 that should not be overlooked, especially by endocrinologists.

### 10.5 Telemedicine

Diabetes is a disease which requires a careful management and communication between patients and providers. During a pandemic, this communication is difficult, highlighting a need to turn towards telemedicine in order to manage patients. Two cases of new-onset type 1 diabetes in Colorado, one adult and one pediatric, highlight the effectiveness of telemedicine.<sup>24</sup> The adult patient used multiple daily insulin injections, and the pediatric patient used a continuous insulin pump. Both patients used continuous glucose monitoring software (Dexcom Clarity and Glooko). By following up with the patient's glucose monitoring online, and checking in with them via e-mail, Zoom video conferencing, and telephone calls, both patients have been effectively managed during the pandemic.<sup>24</sup>

In India, a review of telemedicine guidelines suggests that it is an important tool to use in managing chronic conditions like diabetes.<sup>25</sup> However, more research should be done on the long-term impact of telemedicine on health outcomes. The authors caution that because telemedicine cannot replace the physical examination, at least the first consult should be in-person.<sup>25</sup>

### 10.6 Tools for Health-Care Providers

1. Algorithms based on emerging guidelines: <https://www.covidindiabetes.org/> (website and app available)
2. <https://abcd.care/coronavirus>
  - UK National diabetes inpatient COVID response group
  - Simple, safe, diabetes guidelines for specialists and nonspecialists
  - First set of guidelines—for specialists outlines key requirements vital to maintaining patient safety
  - Second set—for EM physicians/acute admitting teams. Provides algorithm for acute admitting and management of diabetes at the “front door”
3. [https://www.ama-assn.org/practice-management/digital/ama-quick-guide-telemedicine-practice?&utm\\_source=BulletinHealthCare&utm\\_medium=email&utm\\_term=031820&utm\\_content=NON-MEMBER&utm\\_campaign=article\\_alert-morning\\_rounds\\_daily&utm\\_uid=2539335&utm\\_effort=MRNRD0](https://www.ama-assn.org/practice-management/digital/ama-quick-guide-telemedicine-practice?&utm_source=BulletinHealthCare&utm_medium=email&utm_term=031820&utm_content=NON-MEMBER&utm_campaign=article_alert-morning_rounds_daily&utm_uid=2539335&utm_effort=MRNRD0)
  - AMA Guide to Telemedicine

### 10.7 Conclusion

1. Diabetes is the third most common comorbidity in COVID-19 patients, and is associated with more severe disease, increased ICU admission, and a higher risk of death.
2. Diabetes is a multiorgan disease, and there are numerous mechanisms which may make COVID-19 more severe in diabetic patients:
  - Immunocompromised state
  - ACE2 upregulation
  - Precipitation of DKA by SARS-CoV-2 infection.
3. There are no changes to diabetes management guidelines for COVID-19 patients.
4. Glycemic regulation is a major factor in reducing morbidity and mortality.
5. Adrenal insufficiency and subacute thyroiditis are other endocrine manifestations of COVID-19, which should not be overlooked.
6. Telemedicine is key to managing new-onset and chronic diabetes during a pandemic.

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# Dermatological Manifestations of COVID-19



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## List of Abbreviations

EBV	Epstein–Barr virus
PPE	Personal protective equipment
RT-PCR	Reverse transcription polymerase chain reaction

As COVID-19 continues to change our daily lives in unimaginable ways, it also continues to pose challenges to all physicians alike, including dermatologists. Many dermatologists have discovered eruptions and lesions associated with COVID-19 infection and its treatment. This chapter summarizes the latest evidence on dermatological manifestations associated with COVID-19, including the usage of personal protective equipment (PPE)-induced skin injuries in patients and health-care providers. Table 11.1 summarizes the dermatological manifestations of COVID-19.

### 11.1 Overview

The dermatological manifestations associated with COVID-19 infection are lesions characterized as erythematous rash, urticaria, chickenpox-like vesicles, livedo reticularis-like eruptions, chilblain-like lesions, digitate papulosquamous eruptions, and petechiae. One dermatological manifestation that was discovered to be associated with COVID-19 treatment is exanthematous drug eruption characterized by erythematous macules or papules possibly due to antiviral medications given to positively diagnosed COVID-19 patients. Health-care workers and patients have also seen the dermatological impacts from PPE usage such as skin lesions, increased acne, dermatitis, and facial itching.

**Table 11.1** Dermatological COVID-19 Case Table

Dermatological Symptoms	Biological Sex	Age	Ethnicity	Symptom Location	Symptom Characteristics	Diagnostic Test	Patient/s COVID-19 Diagnosis (Positive or Negative)	Treatment of Dermatological Symptoms
Chilblain lesions	Unavailable	All ranges, but mainly median age of 13 and 31 years	Unavailable	Mainly on toes, soles, fingers, extremities, and/or heel	Purpuric, flattened, painful upon palpitation	RT-PCR	Positive; asymptomatic	Unavailable
Livedo Reticularis	Unavailable	Unavailable	Unavailable	Unavailable	Lacy, purple, no associated itching	Unavailable	Positive	Resolved without intervention within 24 h
Exanthematous drug eruption/morbiliform drug eruption	Unavailable	35-year-old in one case	Unavailable	Initially and mainly seen on the trunk; spread to extremities within 24 h	Itchy red/purple rash seen 10 days after antiviral treatment; possibly due to antiviral medications used to combat COVID-19	Unavailable	Positive	Systemic corticosteroids; corticosteroid topical treatment; systemic antihistamines

Digitate papulosquamous eruption	Unavailable	Unavailable	Unavailable	Laterally on the trunk and thighs, upper arms, shoulders, back, periumbilical	Squamous and erythematous patch, scaly thin plaques, poplar lesions could be due to secondary result of immune response against coronavirus	RT-PCR	Positive	Unavailable; patient expired
Petechiae	Male	48-year-old in one case	Unavailable	Systemic distribution on the buttocks, lower abdomen, proximal anterior thighs, popliteal fossae	Pruritic skin lesions	Nasopharyngeal swab RT-PCR	Positive	Unavailable



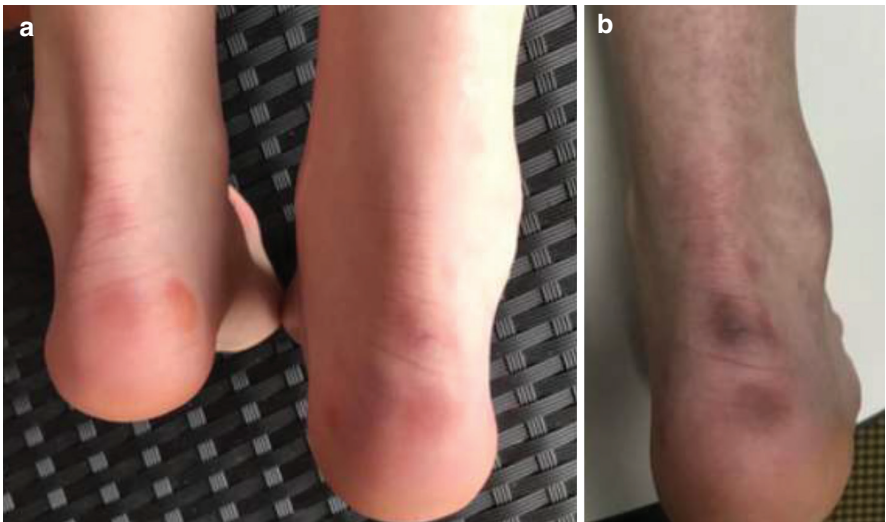
## 11.2 Clinical Manifestations

There are a few significant dermatologic manifestations of COVID-19. Some of the manifestations that have been reported are chilblain lesions, erythematous rashes, skin lesions due to the hypercoagulable state of COVID-19, livedo reticularis-like eruptions, exanthematous drug eruptions or maculopapular rashes, digitate papulo-squamous eruptions, and petechiae.

There have been a series of cases where suspected COVID-19 patients presented with reddish and papular lesions that seemingly resemble chilblains (Figures 11.1–11.4).<sup>1</sup> These lesions were seen in all age ranges, but mainly in children with a



**Figure 11.1** Chilblain lesions on toes and heel.<sup>1</sup>



**Figure 11.2** (a) Papular lesions on heel. (b) Same lesions a week later.<sup>1</sup>

**Figure 11.3** Acral lesion with crust.<sup>1</sup>



**Figure 11.4** Erythematous lesions.<sup>1</sup>



median age of 13 years, and young adults with a median age of 31. After 1 week, these lesions were found to become more purpuric and flattened. They eventually disappeared without intervention. Some patients reported the lesions to be painful when palpated; however, they were not very symptomatic. These lesions were discovered to be mainly located on the toes, soles, fingers, extremities, and/or heel but are commonly referred to as “COVID toes” (Figure 11.5).<sup>1</sup>

**Figure 11.5**

Erythematous-violaceous lesions in the toe.<sup>1</sup>



The patients were asymptomatic, but some reported contact with suspected or infected COVID-19 patients.<sup>1</sup> Two of the patients had a positive diagnosis of coronavirus. The chilblain-like lesions could possibly be a late manifestation of COVID-19. In order to verify if the lesions are related to COVID-19, it is recommended to do a biopsy of them and to possibly perform a reverse transcription polymerase chain reaction (RT-PCR) test, along with an IgM-IgG serological test on patients. These lesions can also help to diagnose COVID-19 patients who are asymptomatic.<sup>1</sup>

In a study of 88 COVID-19 patients in Italy, 20.4% of patients had skin involvement during the viral infection. The lesions were characterized as an erythematous rash in 14 patients, widespread urticaria in three patients, and chickenpox-like vesicles in one patient. The eruptions were primarily located on patients' trunks, and there was little to no associated itching with the lesions. The eruptions were present only for a few days before resolving spontaneously.<sup>2</sup> These types of exanths are commonly seen in many other viral infections such as measles and mononucleosis.

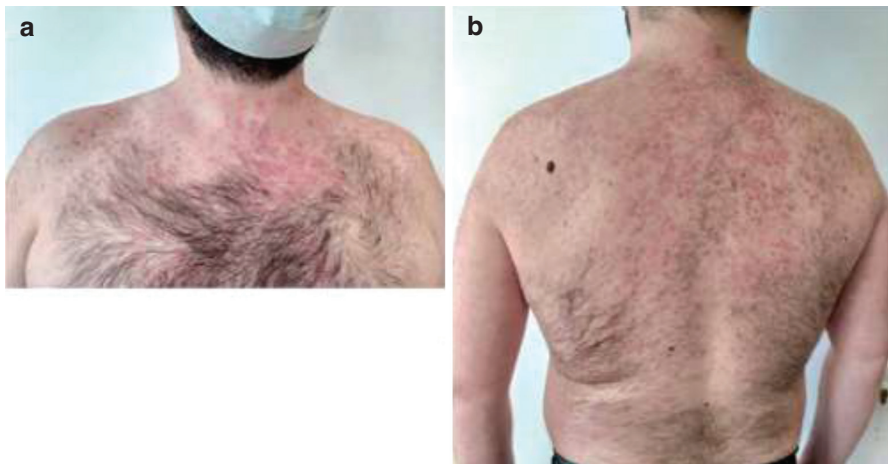
In addition to these viral infection-associated exanths, there have been some reports of skin lesions that are likely due to the hypercoagulable state that many COVID-19 patients are in.<sup>3</sup>

A few cases of a livedo reticularis-like rash have been reported. The patients' lesions are described as lacy and purple, with no associated itching. These eruptions resolved within 24 h in most patients.<sup>4</sup> Livedo reticularis normally occurs due to the interruption of blood flow that leads to deoxygenated blood pooling in the cutaneous venous plexus.<sup>5</sup> If such a livedo reticularis-like rash is occurring in COVID-19 patients, this raises concern for the interruption of blood flow to other organs in addition to the skin. In fact, one of the COVID-19 patients who was reported to have the livedo reticularis-like rash also had hematuria. This may have been due to the

interruption of the kidney's blood supply resulting in glomerulonephritis or cystitis.<sup>5</sup> Thus, it is important for clinicians treating patients with this kind of skin eruption to be wary of other possible symptoms of hypercoagulability.

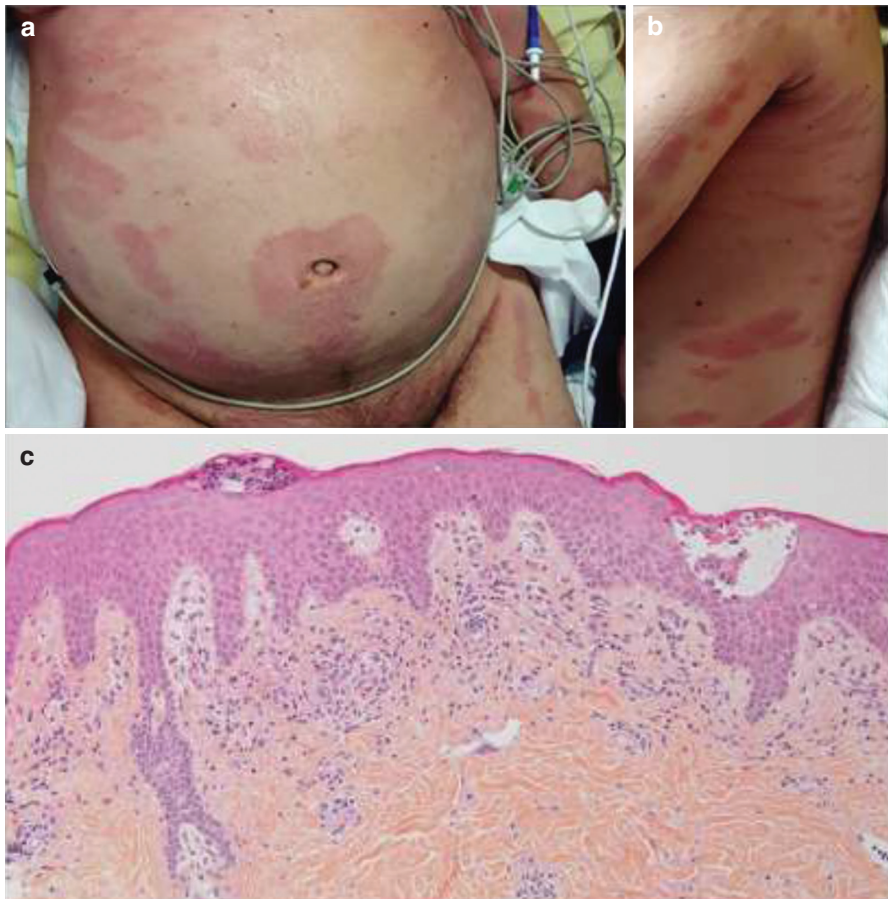
Another possible viral manifestation of COVID-19 is exanthematous drug eruption, or morbilliform drug eruption (Figure 11.6).<sup>6</sup> This immune reaction is characterized by erythematous macules and/or papules that are usually seen in patients with bacterial and viral infections, and about 5 days to 3 weeks after the administration of certain drugs, such as antivirals, anti-hypertensives, anti-inflammatory medications, and antibiotics. However, this condition is mostly seen after administering antiviral medications. Due to the use of lopinavir/ritonavir drug combinations in combating the coronavirus, there have been reports of an increase in maculopapular drug eruptions.

In one example, a 35-year-old, positively infected coronavirus patient was diagnosed with optic neuritis a week before he was admitted to the hospital. He did not present with any symptoms, and reported no history of international travel or exposure to infected COVID-19 patients or patients suspected of having COVID-19.<sup>6</sup> The patient was isolated in the hospital's COVID-19 unit and treated with oral lopinavir/ritonavir 400/100 BID for 10 days. Subsequently, the patient presented with an itchy, maculopapular eruption during his hospitalization. These were initially, and mainly, seen on the skin of the trunk and eventually spread to upper extremities after 24 h. The patient reported to have had no history of contact dermatitis, drug reactions, or other hypersensitivity reactions.<sup>6</sup> In order to treat the morbilliform eruption, dermatologists administered an increased dose of systemic corticosteroids and began corticosteroid topical treatment along with systemic antihistamines. At the 10-day follow-up, there was no evidence of the patient's skin lesions.



**Figure 11.6** (a, b) Morbilliform eruption observed on the trunk and neck. These manifestations are primarily seen on the skin of the trunk.<sup>6</sup>

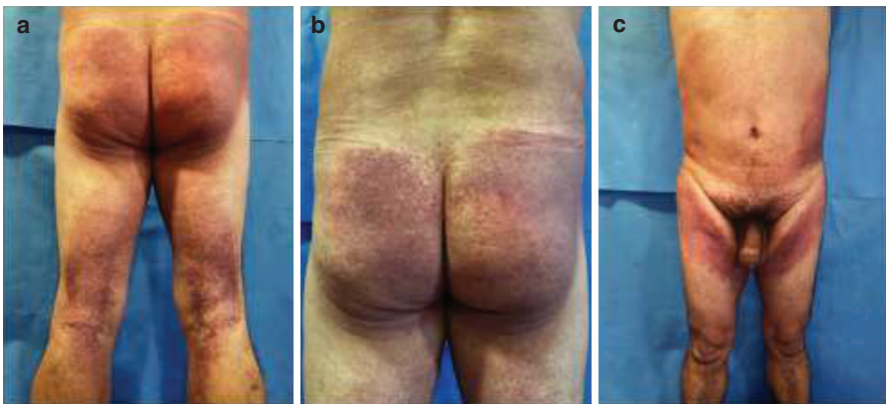
There is some speculation that there could be a direct association between morbilliform eruptions and COVID-19 infection. Furthermore, an example showing this link was observed in the data collected by dermatologists analyzing skin lesions in 88 Italian COVID-19 patients. This data reflected that about one-fifth of patients developed maculopapular eruptions (Figure 11.7).<sup>6</sup> There was also no correlation between the COVID-19 infection severity and the cutaneous findings. Although there are some reports of morbilliform eruptions seen in COVID-19 patients who were taking antiviral medications such as lopinavir and ritonavir, there is no certainty that this type of presentation is only caused by medications.<sup>6</sup> There is suspicion that COVID-19 may be another factor for the morbilliform eruptions that were observed. But the association needs to be examined through further research.<sup>6</sup>



**Figure 11.7** (a) Erythematous squamous lesions with periumbilical patch and lesions on the abdomen and thighs. (b) Skin lesions on the left upper arm and flank.<sup>7</sup> (c) Spongiosis in the epidermis and spongiotic vesicles with aggregates of lymphocytes and Langerhans cells.<sup>7</sup>

A case of digitate papulosquamous eruption was reported during a SARS-CoV-2 infection (Figure 11.8).<sup>7</sup> The patient was admitted to the intensive care unit for acute respiratory distress. The patient was diagnosed with COVID-19 through a nasopharyngeal SARS-CoV-2 RT-PCR. The patient developed a squamous and erythematous periumbilical patch and was later seen to have a rapid progression of other similar digitate scaly thin plaques laterally on the trunk and thighs. Papular lesions were found on the upper arms, shoulders, and back. A skin biopsy of the left shoulder showed spongiotic vesicles with aggregates of lymphocytes and Langerhans cells. RT-PCR was performed on the skin biopsy and was negative for SARS-CoV-2. The patient tested positive for Epstein–Barr virus (EBV) through a blood test. The eruption resolved spontaneously within 1 week; however, the patient eventually died of COVID-19-related illness. It was concluded that the cutaneous rash could be a secondary result of the immune response against the coronavirus, as there was no evidence of a cutaneous drug reaction to cefpodoxime. EBV was not suspected to have caused the cutaneous findings although EBV was found to be reactivated.<sup>7</sup>

A case of petechiae was reported during the COVID-19 outbreak in Madrid, Spain. A 48-year-old man with hypertension presented to the emergency department, where he reported a fever, chest pain, and shortness of breath several days before hospital admission. Three days after the onset of fever, he noticed the appearance of pruritic skin lesions. Petechiae was seen in a symmetric distribution on the buttocks, popliteal fossae, proximal anterior thighs, and lower abdomen (Figure 11.8).<sup>8</sup> A nasopharyngeal swab RT-PCR was performed and resulted in a positive diagnosis for SARS-CoV-2 for this patient. Serologic test results were negative for HIV, hepatitis B virus, hepatitis C virus, and parvovirus B19.<sup>8</sup>



**Figure 11.8** Erythematous macules, papules, and petechiae affecting the popliteal fossa, buttocks, and anterior thighs (a) Posteroinferior view, (b) Close-up view of the buttocks, (c) Anterior view.<sup>8</sup>

### 11.3 PPE Usage Impact on Patients

Although not a direct pathophysiologic effect of the virus, many COVID-19 patients have developed dermatologic issues simply due to increased PPE usage and extensive personal hygiene measures.<sup>9</sup> The resultant friction due to consistent PPE utilization along with the hyper-hydration effects of PPE can result in notable skin lesions. Erythema and scaling have been observed, along with burning, stinging, and itching. Lesions are primarily found on the face due to face masks, with some lesions on the hands due to glove use. Many individuals have amplified personal hygiene measures by washing their hands several times a day, which can result in hand dermatitis (Figure 11.9).<sup>9</sup> In one extreme case, a woman washed her face with 60% ethanol five times per day and wore a face mask for 6 h per day, two measures which resulted in facial redness and papules (Figure 11.10).<sup>9</sup>

**Figure 11.9** Hand dermatitis from excessive hand washing.<sup>9</sup>



**Figure 11.10** Facial erythema and papules in a 42-year-old female patient who disinfected her face with 60% ethanol and used a protective facial mask for 6 h per day.<sup>9</sup>

## 11.4 PPE Usage Impact on Health-care Workers

Health-care workers in particular are uniquely susceptible to PPE-related skin lesions due to the amount of time during which they must wear face masks, gloves, etc. With N95 masks, in particular, many health-care workers report increased acne, dermatitis, and facial itching.<sup>10</sup> Recurrent use of lipid-emulsifying detergents that diminish lipids in the stratum corneum layer of the skin can cause skin dryness. Hand sanitizers can also compromise the stratum corneum layer of the skin due to the lipid-dissolving alcohols.<sup>10</sup>

In order to combat dermatologic reactions to PPE usage and personal hygiene, it is recommended to moisturize the skin and avoid allergens found in disinfectant products containing quaternary ammonium.<sup>10</sup> The most efficient method to combat adverse cutaneous reactions from hygiene practices is to regularly utilize oil-containing emollients after handwashing. In a randomized, double-blind trial of health-care workers who all presented with severe hand irritation, it was seen that the scheduled use of oil-containing lotion was better than creams for improving skin scaling, cracking, and pain in the hands.<sup>10</sup>

It would be beneficial for dermatologists to promote protective methods during the pandemic, such as proper hand-washing procedures, avoiding washing hands with hot water to reduce the possibility of having skin damage, avoiding antibacterial soaps due to them not being superior to non-antibacterial soaps in preventing infections, avoiding chemicals in soaps to reduce the possibility of having allergic reactions, utilizing a 60% alcohol-based hand sanitizer on hands for 20 s if soap and water are unavailable, avoiding sanitizers containing fragrances to reduce allergic skin reactions, and avoiding a direct skin contact with EPA-registered disinfectant products by wearing gloves and cleaning hands afterward to prevent allergic skin reactions.<sup>10</sup> Furthermore, oil-emollient moisturizers to the hands after handwashing can be regularly applied to combat skin damage induced by allergens.<sup>10</sup>

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# Ophthalmological Manifestations of COVID-19



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## List of Abbreviations

COVID-19	Coronavirus disease 2019
PPE	Personal protective equipment
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

## 12.1 Introduction

COVID-19 has changed how ophthalmologists are running their practices and treating their patients. This chapter shares the latest information on the ophthalmological manifestation of COVID-19, and its impact on patients and health-care providers.

## 12.2 Conjunctivitis

The most common, and only, ophthalmic manifestation of the SARS-CoV-2 virus reported is conjunctivitis.<sup>1</sup> Conjunctivitis can present as a first, or only, sign of infection from SARS-CoV-2. All the reports of conjunctivitis associated with SARS-CoV-2 have been “bilateral, mild, follicular conjunctivitis without corneal involvement” with some exceptions.<sup>1</sup> Although initially believed to be a rare manifestation, conjunctivitis is now being believed to be a primary symptom of the SARS-CoV-2 infection.<sup>2</sup> According to an AAAS study, “The estimated proportion of those with ocular symptoms, some consistent with conjunctivitis, ranges widely, from <1% (Centers for Disease Control and Prevention Coronavirus 2019-Associated Hospitalization Surveillance Network) to more than 30%, suggesting that conjunctivitis could be a disease feature and potentially a useful diagnostic sign.”<sup>3</sup>

## 12.3 Precautions

### 12.3.1 Personal Protective Equipment (PPE)

To protect against SARS-CoV-2 during regular office visits, ophthalmologists are recommended by the American Academy of Ophthalmology to continue using the proper disinfecting practices of instruments and offices using bleach- and alcohol-based disinfectants before and after every patient encounter.<sup>1</sup>

Although there is no documented evidence that SAR-CoV-2 can be transmitted via ocular secretions, it may be possible to contract COVID-19 from a COVID-19 patient who has conjunctivitis.<sup>1</sup> Precautions should still be taken such as having one's eyes, mouth, and nose protected using goggles or N95 mask as well as slit-lamp breath shields<sup>1</sup>

### 12.3.2 Chloroquine and Hydroxychloroquine

Regarding the usage of the drugs chloroquine and hydroxychloroquine in response to the COVID-19 pandemic, the American Academy of Ophthalmology warns against the potential of developing irreversible maculopathy if these drugs are taken in high doses over short periods of time.<sup>1</sup>

## 12.4 Testing

Several of the reports of such patients also demonstrated that these patients tested positive for SARS-CoV-2 by detecting its mRNA on RT-PCR on conjunctival swabs.<sup>1</sup> One patient tested positive for SARS-CoV-2 by culturing the virus from an eye swab.<sup>1</sup> Expression of mRNA for ACE has been seen in conjunctival epithelial cells as demonstrated in studies by Zou et al.<sup>4</sup> and Sungnak et al.<sup>5</sup> “One study purported to show that SARS-CoV-2 could infect human conjunctival explants”; however, “its presence in conjunctival epithelium remains controversial” (Table 12.1).<sup>1</sup>

## 12.5 Conclusion

The key takeaways from an ophthalmological point are as follows:

- Patients presenting with conjunctivitis should be tested for COVID-19.
- Patients with COVID-19 may present with conjunctivitis as the only manifestation of COVID-19.
- Those performing eye examinations should use appropriate PPE such as masks, gloves, and gowns.

**Table 12.1** Major Studies and Findings on the Relationship of Ophthalmological with SARS-CoV-2<sup>1</sup>

Study	Findings
<i>Journal of Medical Virology</i> study <sup>6</sup>	Findings: 1/30 hospitalized COVID-19 patients had conjunctivitis and had SARS-CoV-2 RNA in ocular secretions <sup>1</sup> Conclusions: Patients with COVID-19 and conjunctivitis can have infectious viral particles in their tears (verified by case report from China and another from Italy)
Clinical Characteristics of Coronavirus Disease 2019 in China published in the <i>New England Journal of Medicine</i> <sup>7</sup>	Findings: 9/1,099 hospitalized COVID-19 patients had conjunctival congestion from 30 hospitals across China None of the patients were seen by ophthalmologists, and tears were not sampled
Ocular Manifestations of Hospitalized Patient with Confirmed 2019 Novel Coronavirus Disease <sup>8</sup>	Findings: 30-year-old COVID-19 man developed acute follicular conjunctivitis in both eyes 13 days after onset.
SARS-CoV-2 Isolation from Ocular Secretions of a Patient with COVID-19 in Italy With Prolonged Viral RNA Detection <sup>9</sup>	Findings: A 65-year-old woman demonstrated bilateral conjunctivitis 1 day after onset of COVID-19 symptoms. Ocular swabs on day 3 had a presence of viral RNA, and ocular samples were taken every day for 21 total days. Each day ocular swabs were positive for viral RNA. By day 15, the conjunctivitis was improving and it was gone by day 20.
Neurological Manifestions of Hospitalized Patients with COVID-19 in Wuhan, China <sup>10</sup>	Findings: Among the 214 hospitalized COVID-19 patients, 3 had impaired vision, 2 of which had severe disease and 1 had nonsevere disease.f
Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China, published March 31 in <i>JAMA Ophthalmology</i> <sup>11</sup>	Findings: 12/38 hospitalized COVID-19 patients from Hubei, China, had “ocular ‘abnormalities’, characterized most commonly as chemosis and/or secretions” 2 of these patients tested positive for SARS-CoV-2 from conjunctival swabs, 1 of whom had signs of conjunctival hyperemia
The Infection Evidence of SARS-COV-2 in Ocular Surface: A Single-Center Cross-Sectional Study, a study by Zhang et al. <sup>12</sup>	Findings: 2/72 hospitalized COVID-19 patients from Tongji Medical College had conjunctivitis
Ophthalmologic Evidence Against the Interpersonal Transmission of 2019 Novel Coronavirus through Conjunctiva, a paper by Zhou et al. <sup>13</sup>	Findings: 1/63 hospitalized COVID-19 patients from Wuhan had conjunctivitis One patient had tested negative for SARS-CoV-2 using the conjunctival swab test, 2 showed “probable” results, and 1 other patient without conjunctivitis tested positive.

(continued)

**Table 12.1** (continued)

Study	Findings
SARS-CoV-2 Isolation From Ocular Secretions of a Patient With COVID-19 in Italy With Prolonged Viral RNA Detection <sup>14</sup>	Findings: A COVID-19 patient in Italy also had conjunctivitis <sup>1</sup> This patient also had respiratory symptoms, gastrointestinal symptoms, and fever. This patient also tested positive for SARS-CoV-2 using RT-PCR on conjunctival swab test from the 3rd to 21st day of hospitalization & also on the 27th day when the nasal swabs were negative.
Care Home Nurse Tells of Terrifying and Sudden Ways Coronavirus Struck Her Patients, a story from CNN <sup>15</sup>	Findings: Red eye was reported as one of the first symptoms frequently seen among residents in a nursing home in Washington state during a COVID-19 outbreak
Keratoconjunctivitis As The Initial Medical Presentation of the Novel Coronavirus Disease 2019 (COVID-19) <sup>16</sup>	Findings: A patient with unilateral conjunctivitis and a coarse epithelial keratitis tested positive for SARS-CoV-2 using RT-PCR on a conjunctival swab
COVID-19 Emergency In The Cruise's Ship: A Case Report of Conjunctivitis <sup>17</sup>	Findings: One patient had bilateral pseudomembranous conjunctivitis when they got COVID-19 while on a cruise ship
Hemorrhagic Conjunctivitis with Pseudomembranous Related to SARS-CoV-2 <sup>18</sup>	Findings: One hospitalized COVID-19 patient in France had bilateral hemorrhagic, pseudomembranous conjunctivitis

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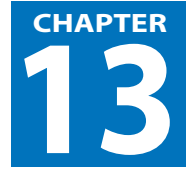
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# Mental Health Manifestations of COVID-19



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## List of Abbreviations

CNS	Central nervous system
COVID-19	Coronavirus disease 2019
ECG	Electrocardiogram
ICU	Intensive care unit
PTSD	Post-traumatic stress disorder
SARS	Severe acute respiratory syndrome

### 13.1 Introduction

One unexplored visible impact of coronavirus disease 2019 (COVID-19) is on the mental health of people—patients, their loved ones, and the general public under nationwide lockdowns. Everyone is affected, whether directly or indirectly, highlighting the massive impact the pandemic has had socially, economically, and psychologically. The focus of this chapter is on the psychological crisis facing people and specific populations, such as health-care workers, patients with underlying mental health disturbances, and patients with COVID-19. This chapter will close with the recommended next steps in addressing current and new issues that may arise.

### 13.2 Pandemics in History and Psychological Impacts

As noted earlier (see Chapter 7), COVID-19 can potentially have multiple effects on the central nervous system (CNS). But the impact and the full scope of effects are not yet well known, including how long they may last. Recently, more evidence is coming out calling for greater mental health impacts and interventions to address the new gaps in care. This section reviews the history of pandemics and psychological impacts.



Over the course of human history, human beings have dealt with many mass disastrous events, including natural disasters, famine, disease, and war, just to mention a few. These have had innumerable effects on the societies it affected, all the way from the individual to the population level. Epidemics and pandemics, in particular, have played significant roles in human history, as evidenced by the Bubonic plague of the Middle Ages and the Spanish flu outbreak of the early 1900s. Within this century, we have already had four major disease outbreaks that have significantly affected the human populace: the severe acute respiratory syndrome (SARS) epidemic of 2003, the H1N1 epidemic of 2009, the Ebola epidemic in 2014, and now the COVID-19 pandemic.

There is a significant body of research that has come out from prior epidemics in this century on the significant effects the epidemics had on mental health at many levels, including those who became sick, the health-care workers caring for them, and the population at large. Published literature after the SARS epidemic, which affected more than 8000 people, resulted in 774 deaths worldwide, and spread to over 30 countries, showed an increased prevalence of persistent psychological symptoms, even months to years after the epidemic had ceased.<sup>1-5</sup> During the SARS epidemic, higher rates of completed suicide by older adult were reported and attributed to possibly social isolation and increased stress and anxiety among the elderly in Hong Kong.<sup>6-8</sup> In addition, high rates of psychosocial disturbances, such as insomnia, depression, anxiety, and post-traumatic stress disorder (PTSD), were reported among those who had survived but also in their family members.<sup>9</sup> Several studies documented substantial psychological distress in health-care workers caring for SARS patients even years after the event.<sup>1, 10, 11</sup> These results are reflected not only in the literature seen after the other epidemics of this century, but also after significant trauma and disasters.<sup>12</sup>

There are two important psychosocial distinctions from general disasters and disease epidemics: the consequences of social isolation and the fear of spreading the contagion if exposed.<sup>10</sup> Quarantines, while a necessary part of disease prevention and mitigation, have serious and long-lasting effects on the mental health of those affected. This was the case when entire cities and villages were quarantined and public health measures were put in place in China and Canada and West Africa during the SARS and Ebola outbreaks, respectively.<sup>13</sup> Furthermore, the absence of social support offering protection during times of stress exacerbates psychological trauma.

Fear, complicated by mistrust, misinformation and the policies that impacted on the regions' cultural and religious beliefs, has been a strong motivator. This can lead to an exponential rise in certain fear-related behaviors that were intended to be that of survival but instead led to increased risk. During the Ebola outbreak, for example, the health-care system highlighted frailties and led to perceived low quality care and lack of trust, leading to harbor and manage loved ones in their own homes.<sup>14</sup>

### 13.3 Effects on Different Populations

A variety of mental health and psychological factors, similar to those that have been seen historically, are expected to occur during, and after, the current COVID-19 pandemic.<sup>15–19</sup> However, unlike in those disease outbreaks, COVID-19 has strained the entire world and has put a lot of stress on many countries. The mental health exacerbations that may be seen now, and after, are not only due to the similar fears and anxieties evoked by the pandemic itself, but also due to the overwhelming stress this pandemic has placed on the health-care system as a whole. Countries such as China, USA, Italy, Iran, and several others that were hit the hardest are finding their populations experiencing psychological distress, including health-care workers, immigrant populations, the elderly, those with underlying mental illness, and many more groups. Thus, it is crucial to understand now who may be at risk for psychological distress and where mental health services need to be directed.

#### 13.3.1 Mental Health in Patients with COVID-19

One population at risk for mental health distress is the patient, who contracts COVID-19. As mentioned before, the fears of spreading the disease and the subsequent social isolation places those who are exposed and who contract COVID-19 under tremendous emotional strain. In some instances, COVID-19 patients need intensive care unit (ICU)-level care, which creates psychological distress. One study from New York found that of those requiring hospitalization, 14.2% were treated in the ICU and 12.2% received invasive mechanical ventilation.<sup>20</sup> ICU-level care, on its own, can create psychological distress. For example, nearly 20% of patients leaving an adult critical care exhibited PTSD, which in turn was related to a higher likelihood of persistent sleep disturbances.<sup>21,22</sup> A non-COVID-19 study reported that patients admitted to intensive care with acute respiratory distress syndrome, anxiety, depression, and PTSD occurred at high levels during the 2-year follow-up period with relatively low rate of remission of symptoms.<sup>23</sup>

Subsequently, those who had been exposed to disease or who may have gotten sick from it have been subject to ostracization and xenophobia if geographical linkages have been placed to the epidemic, leading to increased fear and anxiety among survivors about reintegrating back into society.<sup>24</sup> Thus, it is important to take a multidisciplinary approach to treating patients with COVID-19 to ensure the best-quality care that addresses the mental health needs of the patient as well.

#### 13.3.2 Psychological Health in Patients with Mental Illness

Patients with mental illness are one of the most vulnerable groups due to a degree of stigmatization they receive and the degree of deprivation they encounter; this encompasses other factors such as poverty, poor lifestyle factors, environment, and

unemployment. A number of stressors that include quarantine, isolation, hardship, and the lack of psychosocial approaches to alleviate and optimize their mental health can have negative effects on their mental health. Inpatient psychiatric care and management can be complicated by the lack of movement, liberty, and possible bereavement for patients. Community-based care is likely to have very limited face-to-face consultations, and reduced care contact is likely to negatively impact a patient's mental health and their concordance.

The challenge to pharmacological management becomes increasingly important during coronavirus. The Royal College of Psychiatrists in the United Kingdom has set out clear channels of support for patients and their carers as well as approaches clinicians should consider.<sup>25</sup> The rates of electroconvulsive therapy, for example, a very effective approach to manage certain severe mental illnesses, has fallen in some parts of the world.<sup>26</sup> The presence of psychiatric medications in a patient who becomes positive for COVID-19 requires specialist attention to ensure their respiratory and cardiovascular health is not compromised. Sedation, respiratory depression, electrocardiogram (ECG) changes, and delirium are some of considerations that will need to be taken into account. People with dementia are at greater risk of suffering from delirium and their aftercare needs, as well as of those with other mental illnesses, are paramount for their rehabilitation. Those that are hospitalized and those that require intensive care will need an approach that covers physical, social, and psychological needs to optimize their well-being.

### 13.3.3 Psychological Health in Health-Care Workers

Another high-risk population for psychological distress is the health-care workers themselves. The very nature of health-care work and the high pressure and stress situations health-care workers find themselves in have been known to be psychologically taxing with deleterious consequences to their mental health for quite some time now. In disease outbreaks, the psychological stress and toll it takes is amplified. Health-care workers are already a high-risk group for suicide and mental health disorders, in particular female physicians and physicians in the United States being found to be at higher risk in a review.<sup>27, 28</sup> One study had found that emergency physicians in the United States were found to have higher rates of PTSD.<sup>29</sup>

Other health-care workers, like nurses, are also found to be at higher risk of suicide and mental health disturbances.<sup>30-32</sup> There is evidence within the nursing profession in the United Kingdom, for example, that rates among female nurses are much higher and female health professionals in general are 24% more likely than the national average female.<sup>33</sup>

During the SARS outbreak, for example, multiple investigations were released on the prevalence of mental health disorders in health-care workers, and they found significantly higher rates of post-traumatic stress and psychological disturbances, even years after the epidemic was declared over.<sup>10, 11</sup> Similar findings were reported in health-care workers who had worked through the Ebola epidemic.<sup>18</sup>

Many have come out warning of the coming psychological impact this pandemic will have on health-care workers, and it is important to remember this group as already a high-risk group for mental disturbances, and so appropriate measures should be taken to address the mental health needs of the health-care working community.<sup>34, 35</sup> Two health-care workers in New York City committed suicide from COVID-19-related stress.<sup>36</sup>

### 13.3.4 Psychological Health in the General Population

The wide-ranging impact of this pandemic will affect almost everyone, be it directly or indirectly, in ways we may not yet have anticipated. Those with preexisting mental health issues, who are themselves at risk for poorer physical health outcomes and may be at higher risk of contracting COVID-19 and faring worse than the general population, are themselves at high risk for psychological distress and at risk for exacerbating their underlying mental health issues, be it due to limited access to medications and providers or due to the effects of social isolation from quarantine.<sup>37, 38</sup> Mental health resources before the pandemic were already limited in many countries, and now as more people become affected and are affected on a psychosocial level, those mental health resources will be stretched thin further.

On top of all that, the massive economic impact of this outbreak by itself can lead to massive psychological trauma, as many citizens have lost their jobs, are unable to buy supplies, and are unable to pay their bills, affecting individuals in all age groups on many levels. There is a great risk of increased alcohol and substance misuse during such times of economic strain, which in turn can lead to increased prevalence of intimate partner violence and domestic abuse.<sup>39, 40</sup> Another study on alcoholism was conducted at USC showed the spurt in alcohol sales up to 55% in late March,<sup>41</sup> which, in turn, can affect childhood psychological well-being, and is associated with long-term psychiatric distress.<sup>42</sup> (Holt 2008). In areas of the world with recent histories of disasters, there is already a higher rate of PTSD, anxiety, and more psychological disturbance than can and will be exacerbated by this pandemic.<sup>43, 44</sup> With already a high prevalence of mental health disorders around the world, this pandemic will further worsen the mental health crises that already exist unless we properly anticipate and tackle these issues now.

## 13.4 Next Steps

Considering the severe impact this pandemic has had and will have on the mental health of so many, it is important to create next steps on how to tackle the “parallel epidemic” of mental health illnesses. We have already seen a great response that comes from the expedited implementation and use of virtual technologies, specifically telemedicine, to continue to provide physical and mental health-care services.<sup>45–47</sup> However, these technologies have their limitations, especially when it comes to access to smartphone or broadband technology services, as is seen in the

United States.<sup>48</sup> Often the populations who need these services the most have the lowest amount of access to these technologies and services, so special attention needs to be paid in making these resources available to our most vulnerable populations during such a strenuous time.<sup>49</sup>

In addition, the role of research cannot be underestimated as we try to move past this pandemic and learn from it.<sup>45</sup> Many areas for potential research exist, such as assessing the access to and examining the effectiveness of virtual technology services for providing mental health services, evaluating the psychological impact this pandemic has had on survivors, health-care workers, and the general population at large, and many more possibilities. The important thing is to have learned as much as we can from this pandemic to be able to best respond to the next crisis, whatever that may be.

### 13.4.1 What you can do (Syed Ashraf Imam, PhD; Clinical Psychologist)

The adverse condition of social isolation and loneliness amid this pandemic around the globe is causing people to live under constant fear, stress, and anxiety, which may lead to hypertension, sugar imbalance, dysfunctional metabolism, chronic medical condition, reduced immunity, and other psycho-physical state of being in a vulnerable condition. Simply put, we can experience increased blood pressure, abnormal glucose levels, insomnia, restlessness, skin disease, depression, hopelessness, irritability, aggression, reduced stress tolerance, and onset of other psycho-medical conditions detrimental to our well-being and quality of life. The good news is that we may practice simple things to protect and prevent sickness simultaneously boosting our immune strength with some fresh tools to increase stress tolerance and resiliency.

By now, most of us are pretty well educated about the basic preventive measures such as hand-washing, social distancing, sanitization, social group avoidance, and cleaning. But changing and adapting to small activities mentioned below and planning to adhere to them can make positive change.

1. **Sleep:** Good sleep rejuvenates our mind and body, boosts our immune system, reduces anxiety/fatigue, and improves our capacity to stay healthy and fit on a daily basis. Practice good sleep hygiene, and sleep your regular hours to satisfaction as you did prior to this crisis.
2. **Breathing Exercise:** Relax yourself; sit or lay down comfortably, close your eyes, listen to your breath while you breathe in and out, and feel the bodily changes as you breathe. Diaphragmatic or belly breathing is better than the chest breathing. Inhale from your nose to the count of 5 sec, hold it for 4 sec, and exhale to the count of 7 sec. Repeat 5 cycles to feel the fresh oxygen in your system.
3. **Mindfulness:** Mindfulness is as simple as being aware of yourself and your being in your surroundings. It can be any act of mind and body exercise that brings us back to consciousness and self-realization. Any religious prayer, meditation, devotional ritual, and focused spiritual exercises accompanying

meditation could be practiced as mindfulness exercise. It enhances our sympathetic nerve response by strengthening our brain pathways that strengthen our coping mechanism in case of adverse situations. Practice mindfulness 3–5 times a day.

4. **Physical Exercise:** It is vital for life: stretches, walking, treadmill, gardening, or other physical activities that suits your taste. Spend at least 30–60 min every day to nurture your strength and resiliency.
5. **Nutrition:** Balanced diet/food, natural supplements, and vitamins improve health and immune system.
6. **Hydration:** Drink 3-4 L of plain water at room temperature every day. Water is life and the best drink. Please consult your physician if you have certain medical conditions that restrict/limit the water intake.
7. **Healthy Habits:** It costs nothing and keeps you strong. Stay away from drugs/abusive substances, and limit your caffeine. This is an opportune time to get rid of any addiction.
8. **Positive Relationship:** This is a high time that we focus on building our positive relationship within and beyond our family system. Resolving conflicts by amicable means and appropriate discussion; exploring mutual strength and respect; and building bridges of love, cohesion, and bonding.
9. **Acceptance and Forgiveness:** Acceptance of others as they are and forgive others and/or seeking forgiveness from others brings a reservoir of positive space and energy into our mind. Cleaning up the clutters and debris from the societal bruise such as grudge, hate, shame, and guilt fills the mind with immense positive energy.
10. **Unconditional Love:** Love is potent and powerful; it has the power to melt the mountain. Love yourself, nature, the creator, your family, your significant others, and anything you could imagine. It changes the perspective on how we perceive self and others. Remember, *“What goes around comes around.”*
11. **Mental Health Care:** *“Media distancing”* is the key; limit your time up to 20 min a day to remain updated with the current news. Stay away from tracking mortality and infection spread on an hourly basis. Find out the appropriate app, YouTube videos/programs per your taste that makes you feel better. Share your feelings and emotions with others, and offer them the space where they can do the same; sharing is caring. Be kind to yourself; no crisis stays forever; the days are longer than the nights. Sun comes out every day to spread the sunshine, and embrace it. Ask for and seek professional help; it is not worth suffering in isolation.
12. **Kindness:** *“An act of kindness a day, keep the sickness away.”* Make a plan to do at least one act of kindness each day; this could be as simple as making a phone call to your friend, relatives, and neighbors to check on them. Lend them your ear that they can whisper in. Be generous in providing them comfort, support, and assurance; even verbal support goes a long way.
13. **Reading/Journaling/Hobbies:** Read the book(s) that you always wanted to but had no time. Reading keeps you up, engaged, and fills your mind with wisdom and intellect. Journaling is very cathartic and healing; relieves one from trauma

of the past and soothes your brain. Put down your thoughts and feelings, your daily experience on the piece of paper and feel the refreshing effect it has. Brush your skill and bring your nostalgia back; get involved in the activities and hobbies you loved in the past or continue to nurture the one that you do.

Last but not the least, set your routine and customize your day based upon the aforementioned tips, track your progress, and make change as needed in consonance with your daily activities and responsibilities. Adhere to the discipline and schedule that you set; keep fine tuning it and enjoy. Start your day with a smile and positive attitude; be grateful for what you have and be kind and compassionate to yourself, others, and the world.

At the end, we would like to close with this small recipe to maintain and get along well with our existential “New Normal” called “*Sanity Hymn*”;

*Sanity Hymn*

*By Syed Ashraf Imam, PhD*

Stay away from TV News

Listen to the Radio instead

Do not track Corona religiously

Keep yourself busy; each day is a new day

Set your goal each day & stay focused

We have plenty to do & achieve

Love & protect yourself; you mean a lot

Love your family; they are yours forever

Adore your Parents; they are most precious

Have solid Faith; it matters

Pray as much as is feasible

Check on your relatives and friends

Give charity if you have cushion

Be grateful to God for what you have

Count on Blessings not on misery

Start your day and continue with Smile;

It releases feel-good Neurotransmitters—

Dopamine, endorphins and serotonin, the Stress Busters

Smile optimizes Blood Pressure & Heart Rate

Eat & Drink healthy

Walk/Stretch/Exercise daily

Watch funny, humorous movies

Listen to what soothes your ears

Stay with the Nature, breath fresh

Look at animals/birds and observe their behavior

Trust yourself and the destiny

Take life as it comes, keep it simple & easy

Live for today, tomorrow is gonna be fine

Do whatever lightens & brightens the mood

Cheers!

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# Pediatric Manifestations of COVID-19



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## List of Abbreviations

AAP	American Academy of Pediatrics
ACE2	Angiotensin-converting enzyme 2
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
GI	Gastrointestinal infection
IBI	Invasive bacterial infection
ICU	Intensive care unit
IL-10	Interleukin 10
IgM	Immunoglobulin M
PCR	Polymerase chain reaction
PIMS-TS	Pediatric Inflammatory Multisystem Syndrome temporally associated
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

### 14.1 Overview

The data available at this time demonstrates clear and important differences in coronavirus disease 2019 (COVID-19) infection in children versus adults. It has been shown that COVID-19 affects pediatric patients less frequently than the adult population and, when infection takes place, the disease is milder and the prognosis is better. In the United States, from February 12 to April 2, 2020, Centers for Disease Control and Prevention (CDC)-gathered data reports that only 1.7% of COVID-positive patients were children aged <18 years.<sup>1</sup> This is reassuring to pediatricians because, in fact, 22% of the US population is <18 years old.<sup>2</sup> Additionally, of the COVID-positive children in the United States, about half (49%) were in the age

range of 10–17, the median age was 11 years, and 15% of positive children were infants <1 year.<sup>1</sup> Also of note, 91% of these pediatric patients had exposure to a COVID-19 patient in the household or community.<sup>1</sup>

## 14.2 Clinical Manifestations

Just as the infectivity differs in the pediatric community, so too do the clinical manifestations. The most common presenting symptoms in children were cough and fever, but at a less frequent rate than in adults. In the aforementioned CDC report, 73% of COVID pediatric patients had symptoms of fever, cough, or shortness of breath—which is less than the 93% of adults aged 18–64 years who presented with these symptoms during the same period.<sup>1</sup> This goes to show that children may be COVID-positive and shedding the virus, but only display mild cold symptoms (congestion, rhinorrhea, sneezing) without cough and fever. In fact, available data from China suggests that pediatric patients may have more upper respiratory tract manifestations and nasopharyngeal carriage, as opposed to lower respiratory tract involvement.<sup>3</sup> Therefore, it may be even more important for children to social distance during this pandemic because of the insidious and mild nature of COVID-19 illness in this age group—especially when coupled with the fact that children typically have undeveloped personal hygiene habits.

Other symptoms that providers should be aware of in children include pharyngeal erythema (which was present in 46% of pediatric cases in Wuhan Children’s Hospital<sup>4</sup>) as well as fatigue, conjunctivitis, diarrhea, and vomiting. In fact, some children presented only with gastrointestinal symptoms.<sup>5</sup> *The Pediatric Infectious Disease Journal* reports that children have been shown to have gastrointestinal infection (GI) complaints in up to 57% of human coronavirus infections (including COVID-19), which is more common than in adults.<sup>6</sup>

As mentioned, the prognosis also seems to differ for children. Available data in the United States shows that 5.7–20% of COVID-positive children were hospitalized.<sup>1</sup> Ostensibly, this is a lower rate than adults aged 18–64 years, of whom 10–33% of COVID-positive patients were hospitalized.<sup>1</sup> Intensive care unit (ICU) admissions were also less in the pediatric world: 0.58–2.0% (children) versus 1.4–4.5% (adults).<sup>1</sup> This is all to say that infected children seem to have a more mild presentation and clinical course. In fact, most children will recover within 1–2 weeks from symptom onset.<sup>4</sup>

This being said, the age of the child potentially has an impact on the prognosis. Initial Chinese data shows somewhat of a trend between severity of disease with younger age. The widely referenced study from Dong et al., a series of over 2000 children with suspected or confirmed COVID-19, reported that the proportion of severe and critical cases was 10.6%, 7.3%, 4.2%, 4.1%, and 3.0% for the age group of <1, 1–5, 6–10, 11–15, and ≥16 years, respectively.<sup>5</sup> Therefore, closer follow-up and management is warranted of younger children—with particular attention to infants <1 year.

Likewise, special attention is necessary for children with underlying medical conditions. The CDC details that among 345 children with confirmed COVID-19 and data on underlying conditions, 23% had at least one comorbidity—most commonly moderate-to-severe asthma, cardiovascular disease, immunosuppression, diabetes, and severe obesity with BMI  $\geq 40$  kg/m<sup>2</sup>.<sup>1</sup> This CDC report also states: “Among the 295 pediatric cases for which information on both hospitalization status and underlying medical conditions was available, 28 of 37 (77%) hospitalized patients, including all six patients admitted to an ICU, had one or more underlying medical condition.”<sup>1</sup> Lastly, there were three pediatric deaths in this report, but investigation is still necessary to confirm COVID-19 as the cause.<sup>1</sup>

## 14.3 Newborn and Infant Considerations

### 14.3.1 Mother-to-Child (Vertical) Transmission

At this point, COVID-19 has not been detected in cord blood, amniotic fluid, or placenta. A study in China has shown maternal viremia levels to be only 1%.<sup>7</sup> With low levels of the virus in maternal blood, placental seeding and vertical transmission are unlikely.<sup>8</sup> In a review of 51 pregnant women with COVID-19, there were no cases of intrauterine transmission documented.<sup>8</sup> However, there have been reports of infants having positive nasopharyngeal cultures on days 1 or 2 of life, as well as an increased immunoglobulin M (IgM) level.<sup>8</sup> Nevertheless, IgM studies are known to be a challenging and unreliable way to diagnose many congenital infections. According to a study by Kimberlin et al., “IgM assays can be prone to false-positive and false-negative results, along with cross-reactivity and testing challenges.”<sup>9</sup> Moreover, these early infant infections could have been due to postnatal contact with infected caregivers.<sup>8</sup> In sum, more definitive evidence is needed regarding COVID-19 and vertical transmission.

In terms of delivery outcomes of pregnant women with COVID-19 pneumonia, a study of nine such livebirths provides some valuable information. Reassuringly, these 9 newborns all had 1-min Apgar scores of 8–9 and a 5-min Apgar score of 9–10.<sup>10</sup> Also, the amniotic fluid, cord blood, neonatal throat swab, and breast milk samples from six of these patients were tested for the virus, and all samples were negative.<sup>10</sup>

### 14.3.2 Breastfeeding

The previously mentioned study also has implications for breastfeeding. To reiterate, none of the six COVID-positive mothers had the virus detected in their breast milk. Nevertheless, clearly droplet transmission could occur through the close contact of breast- or bottle-feeding. Therefore, it is currently advised that mothers with confirmed or suspected infection take precautions to prevent transmission during

feeds: hand hygiene and use of a facemask.<sup>11</sup> The other option is to feed the infant expressed breast milk or formula by another healthy caregiver until the mother has recovered.<sup>11</sup> If the mother chooses to pump breast milk, she should wash her hands beforehand and wear a mask during breastfeeding. Optimally, the pumping equipment should be thoroughly cleaned by a healthy person.<sup>11</sup>

## 14.4 Prevention

It is well known that children play a key role in community-based viral transmission, and this may be further augmented in the case of COVID-19 because they have more mild disease that is likely to go undetected, as well as more nasopharyngeal carriage and upper respiratory involvement. Children also have more gastrointestinal symptoms from COVID-19 compared with adults,<sup>6</sup> and there has even been evidence of fecal shedding in the stool for several weeks after diagnosis.<sup>12</sup> From a public health standpoint, the potential fecal–oral transmission of the virus (and its replication in the GI tract) is especially concerning for infants and children who are not toilet-trained.<sup>13</sup>

In terms of disease prevention during this pandemic, many pediatricians are being asked the same questions—which we will address here. Alcohol-based hand sanitizer is safe for children when used according to the information on the Drug Facts label: “there is no cause for concern if children eat or lick their hands after the hand sanitizer has fully dried.”<sup>14</sup> However, it should be kept out of reach of small children and those <6 years of age should be supervised when using the sanitizer.<sup>14</sup> In terms of masks, the CDC recommends cloth face coverings in public places, but they are not recommended for children <2 years of age because of concerns about suffocation.

## 14.5 Diagnosis

The requirements for COVID-19 testing in the pediatric ambulatory setting vary geographically, but generally do not differ from the adult guidelines. Therefore, in the United States, pediatric testing should follow the CDC’s “Priority 1-3” schema: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html>. Of note, asymptomatic children, regardless of high-risk medical conditions or household contacts, should not be tested. There are many clinical pathways for screening of children during the pandemic, but we will include the algorithms posted by the Children’s Hospital of Philadelphia:

- Ambulatory Setting: <https://www.chop.edu/clinical-pathway/2019-novel-coronavirus-ambulatory-clinical-pathway>.
- Inpatient Setting: <https://www.chop.edu/clinical-pathway/recommendations-sars-cov-2-testing-clinical-pathway>.

Children with fever and no other symptoms are not a high-priority group for COVID testing according to the CDC. However, infants with isolated fever admitted

to rule out invasive bacterial infection (IBI) could also be tested for COVID-19 because young infants have been COVID-positive with fever as their only manifestation.<sup>15</sup> Testing this group would also stop potential spread of the virus in the hospital.

In regard to auxiliary testing, laboratory findings are often normal in pediatric COVID-positive patients, but may include leukopenia, lymphocytopenia, and increased level of procalcitonin or C-reactive protein (CRP).<sup>16</sup> In terms of imaging, pediatric chest radiographs vary from unremarkable to bilateral consolidation,<sup>17</sup> and imaging findings may even be present before symptom onset.<sup>18</sup>

## 14.6 Management

### 14.6.1 Outpatient

If the child has suspected or confirmed COVID-19 infection, has mild symptoms, and does not have any of the aforementioned comorbidities, he or she should be managed at home.<sup>16</sup> The recommended at-home supportive care is similar for any other viral respiratory illness with a heightened focus on prevention of transmission to others. There should be close follow-up with these patients. Monitor for any signs of clinical deterioration, which in infants could manifest itself as central cyanosis, grunting, or difficulty with breast/bottle-feeding.

Below are some useful links from the American Academy of Pediatrics (AAP) to provide to families during the pandemic:

- “Simple Ways to Entertain & Boost Your Baby’s Development at Home”: <https://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Simple-Ways-to-Entertain-and-Boost-Your-Babys-Development-at-Home.aspx>
- “Social Distancing: Why Keeping Your Distance Helps Keep Others Safe”: <https://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Social-Distancing-Why-Keeping-Your-Distance-Helps-Keep-Others-Safe.aspx>
- “Breastfeeding During COVID-19 Pandemic”: <https://www.healthychildren.org/English/ages-stages/baby/breastfeeding/Pages/Breastfeeding-During-COVID-19.aspx>
- “Getting Children Outside While Social Distancing for COVID-19”: <https://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Getting-Children-Outside.aspx>
- “Parenting in a Pandemic: Tips to Keep the Calm at Home”: [https://www.healthychildren.org/English/family-life/family-dynamics/communication-discipline/Pages/Positive-Parenting-and-COVID-19\\_10-Tips.aspx](https://www.healthychildren.org/English/family-life/family-dynamics/communication-discipline/Pages/Positive-Parenting-and-COVID-19_10-Tips.aspx)
- “COVID-19: Information for Families of Children and Youth with Special Health Care Needs”: <https://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/COVID-19-Information-for-Families-of-Children-and-Youth-with-Special-Health-Care-Needs.aspx>



## 14.6.2 Inpatient

“Severe” COVID-19 infection, according to Chiotos et al., is defined as “a new significant requirement for supplemental oxygen (or an increased requirement from baseline) without the need for new or increased non-invasive or invasive mechanical ventilation.”<sup>19</sup> It has been described that this group tends to recover with supportive care alone—which is generally considered the mainstay of treatment for COVID-19 in children.<sup>16</sup>

Chiotos et al. define “critical” disease in a child with “new or increased requirement for invasive or non-invasive mechanical ventilation, sepsis, or multi-organ failure; or rapidly worsening clinical trajectory that does not yet meet these criteria.”<sup>19</sup> This group generally has failed supportive therapy to some extent and, therefore, could benefit from antiviral medication.<sup>19</sup> The Pediatric Infectious Disease Society has endorsed the Chiotos et al.’s report, which has a final recommendation of the following: “A decision-making framework for antiviral therapy that weighs risks and benefits based on disease severity as indicated by respiratory support needs, with consideration on a case-by-case basis of potential pediatric risk factors for disease progression.”<sup>19</sup> If antiviral is indicated, then remdesivir is the preferred agent.<sup>19</sup> Hydroxychloroquine could also be considered if remdesivir is contraindicated or unavailable.<sup>19</sup>

There are many clinical pathways regarding the inpatient treatment of children during the pandemic, but we will include the algorithms posted by the Yale New Haven Children’s Hospital:

- Link #1: <https://www.ynhh.org/childrens-hospital/medical-professionals/clinical-pathways.aspx>
- Link #2: (navigate to the “Pharmacologic Treatment” tab) <https://www.lucid-chart.com/documents/embeddedchart/7a86fcb7-d313-4313-bd66-f069517fbd66>

## 14.7 Discussion

From a pathophysiologic perspective, why do children have lower frequency of infection and more mild disease from COVID-19? This very important clinical question can and should propel our research forward in order to help us to understand more about this virus and its infectivity. Current theories include a less intense immune/cytokine response from children toward the virus as opposed to adults,<sup>20</sup> an interference in respiratory epithelium of young children that causes a lower viral load,<sup>16</sup> or perhaps that the angiotensin-converting enzyme 2 (ACE2) receptor is expressed differently in the respiratory tract of children versus adults.<sup>21</sup>

From a public health standpoint, we would like to address school and daycare openings. These decisions are clearly very difficult, but those responsible ought to be informed of the differences of this virus in children versus adults. A

decision based on general population data alone would discount the impact that children have as vectors for this virus and could potentially risk another rise of this pandemic. Children have a more insidious nature of active disease, because it is milder, tends to have more upper-respiratory and gastrointestinal involvement, and is less likely to present with fever and cough than in adults. The risk of transmission in the community is compounded by children who are not toilet-trained or have underdeveloped personal hygiene habits. Therefore, children are both more likely to be unknowingly sent out of the home while shedding the virus and more likely to spread it while away. Of course, decisions of this magnitude must be weighed against the economic burden on families and nations. Moreover, it is self-evident that schools are fundamental to child development and well-being, which also must be considered when planning the timing for school re-entry.

Lastly, we must qualify the data presented in this chapter by stating that all of the referenced studies and reports have their limitations given the newness and acuteness of this crisis. Our knowledge of this virus is limited and evolving daily. We hope this summary acts as a springboard for future research and investigation.

## **14.8 Update 1: Pediatric Multisystem Inflammatory Syndrome Potentially Associated with COVID-19**

There is a rising concern in the pediatric community regarding a potential multi-system inflammatory disease that is related to COVID-19. On April 27, 2020, the Paediatric Intensive Care Society of the UK released a statement about a “small rise in the number of cases of critically ill children presenting with an unusual clinical picture.”<sup>22</sup> This alert described pediatric patients presenting with clinical manifestations similar to toxic shock syndrome and atypical Kawasaki disease “with blood parameters consistent with severe COVID-19 in children.”<sup>22</sup> These parameters appear to be high CRP, high erythrocyte sedimentation rate (ESR), and high ferritin.<sup>22</sup> The report continued: “Abdominal pain and gastrointestinal symptoms have been a common feature as has cardiac inflammation.”<sup>22</sup> The latter may present as myocarditis with increased levels of troponin and pro-BNP, and may even “have an appearance of their coronary arteries in keeping with Kawasaki disease.”<sup>22</sup>

The Royal College of Paediatrics and Child Health later provided the following case definition for this multisystem inflammatory syndrome:<sup>23</sup>

1. “A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease.”<sup>23</sup>

2. “Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).”<sup>23</sup>
3. “Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) testing may be positive or negative.”<sup>23</sup>

On May 4, 2020, the New York City Health Department released a similar statement describing 15 pediatric cases (aged 2–15 years) compatible with this same disease in New York City hospitals. According to this report, “All patients had subjective or measured fever and more than half reported rash, abdominal pain, vomiting, or diarrhea.” Of note, respiratory symptoms were reported in less than half of these patients. In these cases, PCR results for SARS-CoV-2 also varied. Therefore, the International PICU-COVID-19 Collaboration now refers to this emerging syndrome as “Pediatric Multi-System Inflammatory Syndrome Potentially Associated with COVID-19,”<sup>24</sup> and they have laid out some key takehome points:<sup>24</sup>

- “The disease is rare.”<sup>24</sup>
- “Clinicians who suspect a case should consult promptly with pediatric infectious disease, rheumatology, or critical care specialists.”<sup>24</sup>
- “Because some children get sicker rapidly, they should be cared for in hospitals with tertiary pediatric/cardiac intensive care units.”<sup>24</sup>
- “Laboratory evaluation should include the measurement of sequential inflammatory markers, including complete blood count/differential, CRP, ESR; coagulation parameters, including D-dimer and ferritin; liver function markers; and a cytokine panel. Children should have antibody testing in addition to PCR testing for SARS-CoV-2, since many children are antibody-positive even when PCR-negative.”<sup>24</sup>
- “Children with this syndrome should have serial echocardiograms, including a detailed assessment of the coronary arteries. Many to date have been found to have low heart function, and some have enlargement of the coronary arteries. Children with serious cardiac complications should be followed longer term.”<sup>24</sup>

Why this is occurring is largely unexplained. There is speculation that this syndrome is due to an acquired immune response to COVID-19, but it is still a mystery at this point. In regard to an etiology, cardiologist and international expert on Kawasaki disease Jane Newburger, MD, MPH states: “If you look at the curves, COVID-19 has plateaued, but there’s an exponential rise in this secondary type of shock syndrome...It is even possible that the antibodies that children are making to SARS-CoV2 are creating an immune reaction in the body. Nobody knows.”<sup>24</sup>

More research on this topic is both necessary and forthcoming. For now, it is important that health-care providers be aware of the existence of this disease in children—particularly during this time of pandemic.

## 14.9 Update 2: July 1, 2020

Here, we will provide the key pediatric updates to this ever-evolving pandemic crisis. We will list the updates in bullet-point form and provide links to important websites and articles.

Last updated on 6/25/2020, the AAP has issued the following statement regarding guidance for school re-entry: "...the AAP strongly advocates that all policy considerations for the coming school year should start with a goal of having students physically present in school. The importance of in-person learning is well-documented, and there is already evidence of the negative impacts on children because of school closures in the spring of 2020."<sup>25</sup> The full AAP document outlines social distancing and mask use at schools, testing and temperature checks at schools, as well as bussing, cafeteria/mealtime, and playground recommendations. The full statement can be found here: <https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/covid-19-planning-considerations-return-to-in-person-education-in-schools/>.

Published June 8, 2020, the investigation by Whittaker et al outlines the clinical characteristics of children with Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS). This was a case series of 58 children admitted to eight different hospitals in England. Briefly, the major results were as follows: "Of these children, all had fever and non-specific symptoms, such as abdominal pain (31[53%]), rash (30[52%]), and conjunctival injection (26[45%]); 29(50%) developed shock and required inotropic support or fluid resuscitation; 13(22%) met diagnostic criteria for Kawasaki Disease; and 8(14%) had coronary artery dilatation or aneurysms."<sup>26</sup> Thus, the key takeaways here are that children with this disease have a wide range of signs, symptoms, and severity and that, when you compare PIMS-TS to Kawasaki disease and Kawasaki disease shock syndrome, you find that this disorder is unique from other pediatric inflammatory entities. For more information on how, visit the full JAMA article here: <https://jamanetwork.com/journals/jama/fullarticle/2767209>.

Published in JAMA on June 3, 2020, the case series investigation by Wu et al provides our newest data from Wuhan—with particular attention given to the immunologic features of pediatric patients with COVID-19. The full text can be found here: <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766670>.

In brief sum, they examined 157 pediatric patients with COVID-19 and found that systemic inflammation rarely occurred, which importantly is different from the aggravated inflammatory responses often seen in adults with COVID-19.<sup>27</sup> <https://pccsociety.uk/covid19/> They also found that moderate disease had higher interleukin 10 (IL-10) levels and lower neutrophil levels than patients with more mild disease. They concluded: "The results of this study suggest that dysregulation of immune response may be involved in the pathologic process of COVID-19; gaining a deeper understanding of the role of neutrophils, CD4+ T cells, and B cells in the pathogenesis of severe acute respiratory syndrome coronavirus 2 infection could be important for the clinical management of COVID-19."<sup>27</sup>

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# Radiology of Chest Imaging in COVID-19

## CHAPTER 15

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### List of Abbreviations

ARDS	Acute respiratory distress syndrome
CMR	Cardiovascular magnetic resonance
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CXR	Chest X-rays
MERS	Middle East respiratory syndrome
MRI	Magnetic resonance imaging
RSNA	Radiological Society of North America
RT-PCR	Reverse transcription polymerase chain reaction
SARS	Severe acute respiratory syndrome
WHO	World Health Organization

### 15.1 Introduction

The first two decades of the 21st century have been marked by the emergence of three novel coronal viral illnesses with an unique set of systemic clinical and radiological manifestations: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and coronavirus disease 2019 (COVID-19). In this chapter, we briefly touch on the radiological findings of SARS and MERS, and discuss the common radiological manifestations of COVID-19.

### 15.2 Radiological Manifestations of SARS and MERS

SARS and MERS are known to have an abnormal initial chest screening in at least 80% of infected patients. In SARS, early findings include ground-glass opacification or consolidations, which are predominantly ill-defined, unilateral, peripherally distributed with a propensity for the lower lung zones. The abnormalities are focal



in 50% of cases, multifocal in 40%, and diffuse in 10%. As SARS progresses, the findings become progressively multifocal and spread bilaterally over the course of 2 weeks. In one-fourth of patients, findings can remain focal or unilateral. Computed tomographic scan (CT) findings typically demonstrate interstitial ground-glass opacity early in the course of disease.<sup>2</sup>

In MERS, initial radiographic findings include ground-glass opacification or consolidations, which are predominantly ill-defined, multifocal, and within the lower lung zones. The opacities may extend to perihilar and upper lobes as the disease continues. As in SARS, CT for MERS also typically demonstrates ground-glass opacities in the basilar and peripheral lung zones, interlobular septal thickening, air-space consolidation, and rarely, pleural effusions. After recovery, patients with disease can suffer from instances of fibrosis.<sup>1, 2, 3</sup>

Studies comparing SARS, MERS, and COVID-19 have found significant similarities with some differences. All three diseases upon initial presentation to hospitals are found to have abnormal initial lung chest X-ray findings in at least 69%–85% of patients. Common radiographic and CT findings include ill-defined ground-glass opacification or consolidation with a propensity of the disease to be peripheral and basilar. Pneumothorax, cavitation, and pleural effusions are rare. Similarities also include a disease progression toward multifocal airspace consolidation and acute respiratory distress syndrome (ARDS) with worsening of pulmonary disease. Notable differences between SARS, MERS, and COVID-19 include the greater likelihood of bilateral and multifocal lung involvement earlier with MERS and COVID-19 as compared with SARS. Table 15.1 summarizes some clinical and initial hospital radiological presentations of these diseases.<sup>2</sup> We will discuss the radiographic and computed tomographic findings of COVID-19 in greater detail in subsequent sections.

## 15.3 Radiological Findings of COVID-19

### 15.3.1 Chest X-Rays (CXR)

Chest radiographs may show no abnormality with mild or early infection with SARS-CoV-2. With progression of pulmonary infection, hazy interstitial opacities often with ground-glass appearance develop. These tend to be of bilateral, peripheral, and basilar predominance. This distribution of this opacity is similar to that demonstrated on CT but is more difficult to detect, requiring careful scrutinization. Airspace consolidation may also develop and present as denser areas of opacity. Worsening of lung disease may lead to an ARDS. The presence of a significant pleural effusion is uncommon.

One study from Hong Kong evaluated the radiographs of 64 COVID-19 patients admitted to a hospital. This study showed that baseline chest radiography was positive in 69% of patients as compared to 91% for initial reverse transcription

**Table 15.1** Brief Summary of Clinical & Radiological Presentations of Novel Coronaviruses. Radiology Perspectives of COV 19, Lessons Learned, AJR May 2020<sup>2</sup>

Feature	SARS	MERS	COVID-19
Clinical Sign or Symptom			
Fever or chills	Yes	Yes	Yes
Dyspnea	Yes	Yes	Yes
Malaise	Yes	Yes	Yes
Myalgia	Yes	Yes	Yes
Headache	Yes	Yes	Yes
Cough	Dry	Dry or productive	Dry
Diarrhea	Yes	Yes	Uncommon
Nausea or vomiting	Yes	Yes	Uncommon
Sore throat	Yes	Uncommon	Uncommon
Arthralgia	Yes	Uncommon	
Imaging finding			
Acute phase			
Initial imaging			
Normal	15–20% of patients	17% of patients	15–20% of patients
Abnormalities			
Common	Peripheral multifocal airspace opacities (GGO, consolidation, or both) on chest radiography and CT	Peripheral multifocal airspace opacities (GGO, consolidation, or both) on chest radiography and CT	Peripheral multifocal airspace opacities (GGO, consolidation, or both) on chest radiography and CT
Rare	Pneumothorax	Pneumothorax	Pneumothorax
Not seen	Cavitation or lymphadenopathy	Cavitation or lymphadenopathy	Cavitation or lymphadenopathy
Appearance	Unilateral, focal (50%); multifocal (40%); diffuse (10%)	Bilateral, multifocal basal airspace on chest radiography or CT (80%); isolated unilateral (20%)	Bilateral, multifocal, basal airspace; normal chest radiography findings (15%)

(continued)

**Table 15.1** (continued)

Feature	SARS	MERS	COVID-19
Follow-up imaging appearance	Unilateral, focal (25%); progressive (most common, can be unilateral and multifocal or bilateral with multifocal consolidation)	Extension into upper lobes or perihilar areas, pleural effusion (33%), interlobular septal thickening (26%)	Persistent or progressive airspace opacities
Indications of poor prognosis	Bilateral (like ARDS), four or more lung zones, progressive involvement after 12d	Greater involvement of the lungs, pleural effusion, pneumothorax	Consolidation (vs. GG0)
Chronic phase			Unknown, but pleural effusion and interlobar septal thickening have not yet been reported
Transient reticular opacities <sup>a</sup>	Yes	yes	
Airtrapping	Common (usually persistent)		
Fibrosis	Rare	One-third of patients	Not yet reported

ARD, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; GG0, ground-glass opacity; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

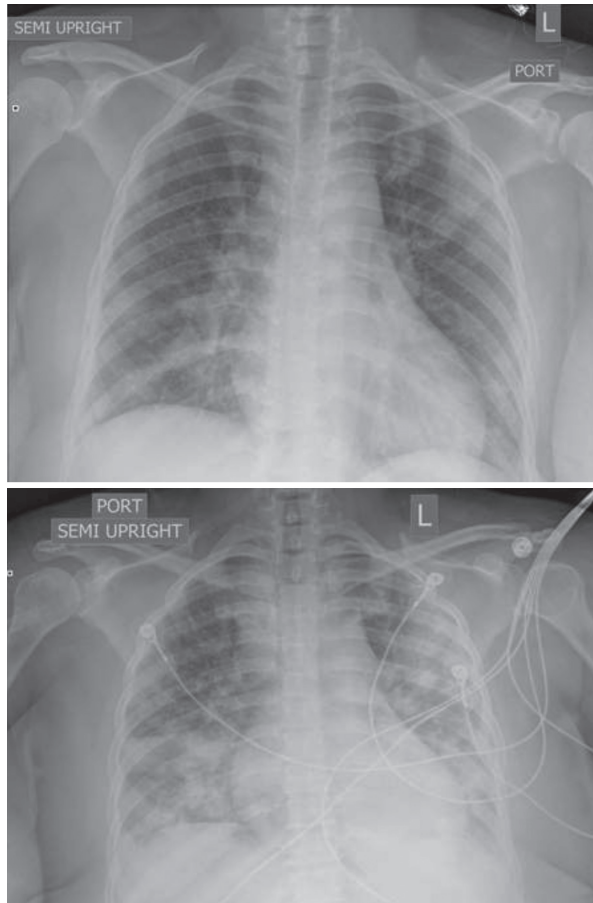
<sup>a</sup>Over a period of weeks or months.

polymerase chain reaction (RT-PCR) test for COVID-19 and that chest radiographic abnormalities preceded a positive RT-PCR test in only 9% of patients. Additionally, the study demonstrated that the worst interstitial opacity on CXR occurred 10–12 days after the onset of respiratory symptoms.<sup>4</sup>

Another study evaluated the initial chest radiographs of 636 COVID-19 patients at urgent care centers in New York City and New Jersey. This study demonstrated that 42% of the initial chest radiographs on these patients were positive. As may be expected, patients presenting to urgent care centers are less sick than patients presenting to hospitals, and a higher percentage of chest radiographs may be normal in outpatient settings.<sup>5</sup>

Another study performed in New York City evaluated 338 young and middle-aged adults (between ages 21 and 50 years) who presented to the emergency room with a positive test for COVID-19 on RT-PCR. The authors focused on correlating initial radiographic findings with hospitalization and intubation.<sup>6</sup> They divided the lungs into 6 zones: a lower zone, middle zone, and upper zone on each side. Each lung zone was given a binary score with airspace opacity present equaling 1 and absence of airspace opacity equaling 0. The maximum score possible was therefore 6. They found that a chest radiograph severity score greater than or equal to 2 was

**Figure 15.1** Middle-aged female presented with nausea, vomiting, and cough, and diagnosed by RT-PCR with COVID-19. Top image shows an initial chest radiograph with mild bilateral ground-glass airspace opacity. Bottom image shows the follow-up chest radiograph 3 days later. There is now worse denser more consolidative airspace opacity within the bilateral lungs.



associated with hospital admission and that among these patients, a chest radiograph severity score greater than or equal to 3 was an independent predictor of the patient becoming intubated (Figure 15.1).<sup>6</sup>

### 15.3.2 Computed Tomography

The Fleischner Society is an international multidisciplinary medical society for thoracic radiology and has made a glossary of terms for thoracic imaging. According to their glossary, the term “ground-glass opacity” is an area of hazy increased lung opacity within which margins of pulmonary vessels may be indistinct.<sup>7</sup> On CT, it appears as hazy increased opacity of the lung with preservation of bronchial and vascular margins. Ground-glass opacity is less opaque than consolidation, in which bronchovascular margins are obscured.

On CT, early COVID-19 pneumonia characteristically presents as interstitial, ground-glass opacity most often rounded with bilateral, peripheral, and basilar predominance. A crazy-paving pattern has also been described. According to the Fleischner Society glossary, a crazy-paving pattern appears as thickened interlobular septa and intralobular lines superimposed on a background of ground-glass opacity resembling irregularly shaped paving stones.<sup>7</sup> Additionally, a reversed halo sign may be present. A reversed halo sign is a focal rounded area of ground-glass opacity surrounded by a ring of consolidation.<sup>7</sup> There may represent areas of microvascular dilatation within areas of ground-glass opacity.<sup>8</sup> With progression of lung disease, airspace consolidations may develop. Finally, in later stages, ARDS may develop, often leading to intubation. Imaging findings not typical of COVID-19 pneumonia include isolated lobar or segmental consolidation, numerous small nodules, pulmonary parenchymal cavitation, a significant pleural effusion, and prominent mediastinal lymphadenopathy.

It is important to keep in mind that very early in the course of disease, CT chest may be normal. One retrospective study evaluated 121 symptomatic patients infected with SARS-CoV-2 based on RT-PCR from four centers in China during the months of January and February 2020.<sup>9</sup> This study evaluated common CT findings in relationship to the time between onset of patient symptoms, typically fever and/or cough, and time of initial CT. Early phase was defined as a CT performed within the first 2 days of onset of symptoms, intermediate phase was defined as a CT performed between 3 and 5 days of onset of symptoms, and late phase was defined as a CT performed between 6 and 12 days of onset of symptoms. 56% of patients who were imaged with CT in the early phase had a normal chest CT. With a longer time period between the onset of symptoms and the initial CT, typical CT findings of COVID-19 pneumonia were more often present. Bilateral lung disease was demonstrated in 28% of patients imaged during the early phase of disease, 76% of patients imaged during the intermediate phase of disease, and 88% of patients imaged during the late phase of disease.

On the other hand, it is also known that CT findings may be present preceding symptom onset. One study evaluated chest CT findings of 104 people who tested positive for COVID-19 with RT-PCR who were on board the cruise ship “Diamond Princess” which had docked in Japan.<sup>10</sup> 73% (76/104) of infected persons were asymptomatic, and 54% (41/76) of these people had opacities in the lungs on CT. There was more ground-glass opacity than consolidation in these people and milder extent of lung opacities compared with those who had symptomatic infection.

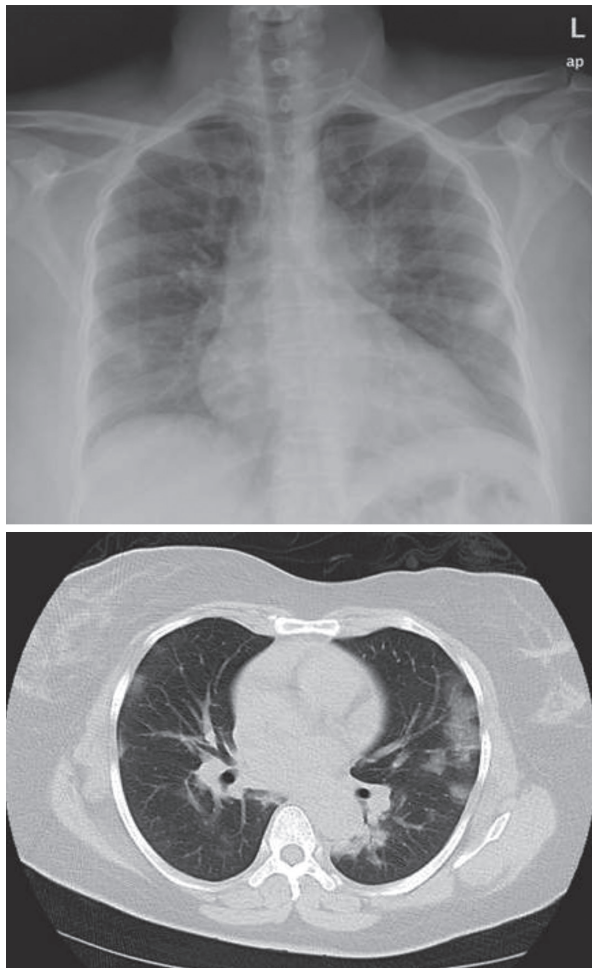
Salehi et al reported on the CT findings of COVID-19 pneumonia utilizing an extensive literature search of PubMed, Embase (Elsevier), Google Scholar, and World Health Organization databases.<sup>11</sup> 919 patients with COVID-19 were included in the final review. The most common finding on initial CT was bilateral multilobar ground-glass opacity which had a peripheral or posterior distribution and was most prevalent in the lower lobes. Follow-up CT demonstrated an increase in ground-glass opacity lesions in both number and size and ground-glass opacity progressively turning into consolidation, septal thickening, and crazy-paving pattern with the worst disease on CT seen approximately 10 days after the onset of symptoms. Disease either regressed or progressed to ARDS, which was the most common reason for transfer of patients to the ICU and the major cause of death. Imaging corresponding

to the improvement of patient symptoms most often occurred after 2 weeks of disease and included gradual improvement and resolution of consolidation and decreased number of pulmonary lesions and number of pulmonary lobes involved.

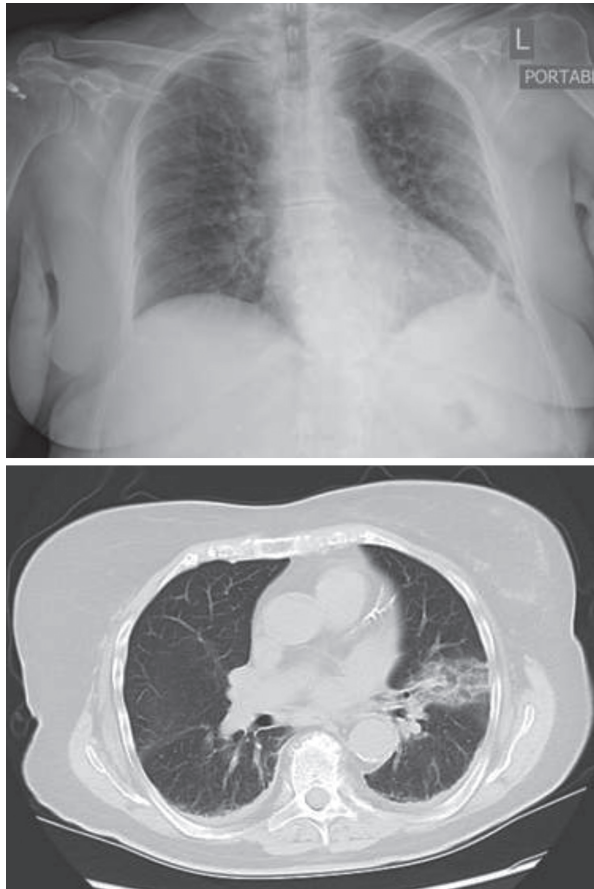
Another study evaluated the temporal changes of pneumonia as seen on CT in 90 patients with COVID-19 pneumonia who were admitted to the hospital.<sup>12</sup> 70 patients were discharged from the hospital at the end of the study with criteria being significant improvement in respiratory symptoms, afebrile for at least 3 days, imaging improvement of disease, and 2 consecutive negative RT-PCR laboratory results at least 24 hours apart. 94% (66/70) of patients discharged had residual disease on CT with ground-glass opacity (60%, 42/70) being the most common finding and pure ground-glass opacity without consolidation (74%, 31/42) being the most common subtype.

Acute pulmonary embolism is not unusual in patients with COVID-19 pneumonia. One study demonstrated 23% of patients who had severe clinical COVID-19 pneumonia and had undergone CT pulmonary angiography, had acute pulmonary embolism in addition to pneumonia (Figures 15.2–15.7).<sup>13</sup>

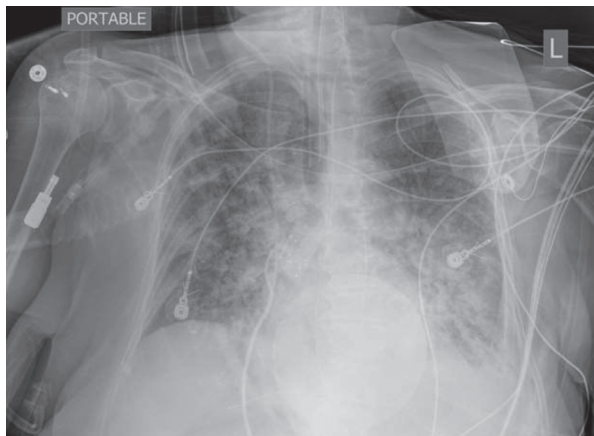
**Figure 15.2** Middle-aged female presented with cough and diagnosed by RT-PCR with COVID-19. Top image shows initial chest radiograph with bilateral mild interstitial opacities, worst in the left upper lobe. Bottom image shows same day CT with typical findings of COVID-19 pneumonia with bilateral peripheral ground-glass airspace opacities and an area of denser consolidation in the left lower lobe.



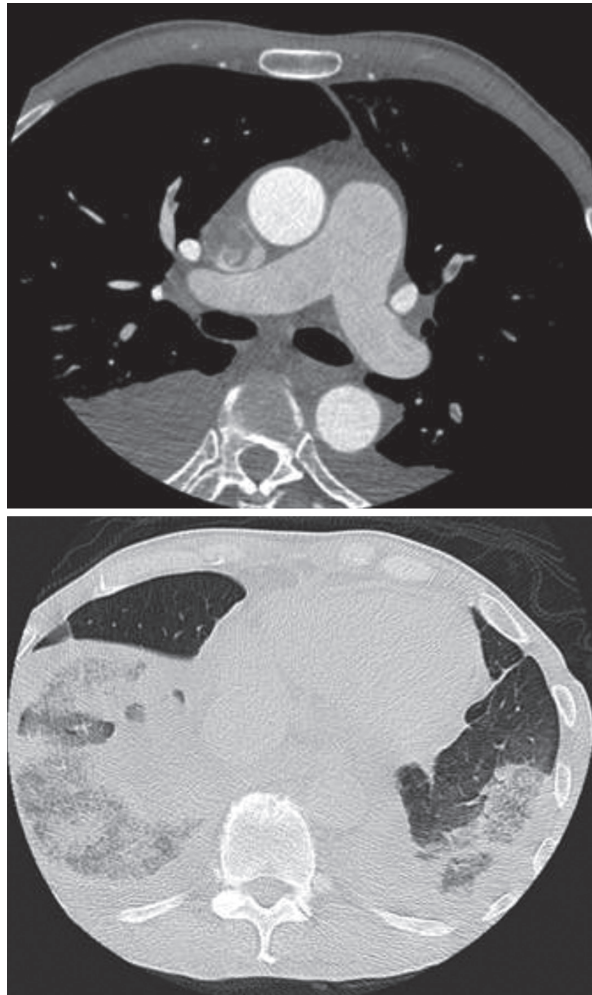
**Figure 15.3** Elderly female presented with fever and diarrhea, and diagnosed with COVID-19 by RT-PCR. Top image shows an initial chest radiograph with mild ground-glass opacity in the left lung. Bottom image shows same day CT chest with corresponding opacity in the lingula.



**Figure 15.4** Same patient as in Figure 15.2. Chest radiograph taken 9 days later on day of death. There are support lines and tubes. There is very significantly worse denser more consolidative airspace opacity within the bilateral lungs.

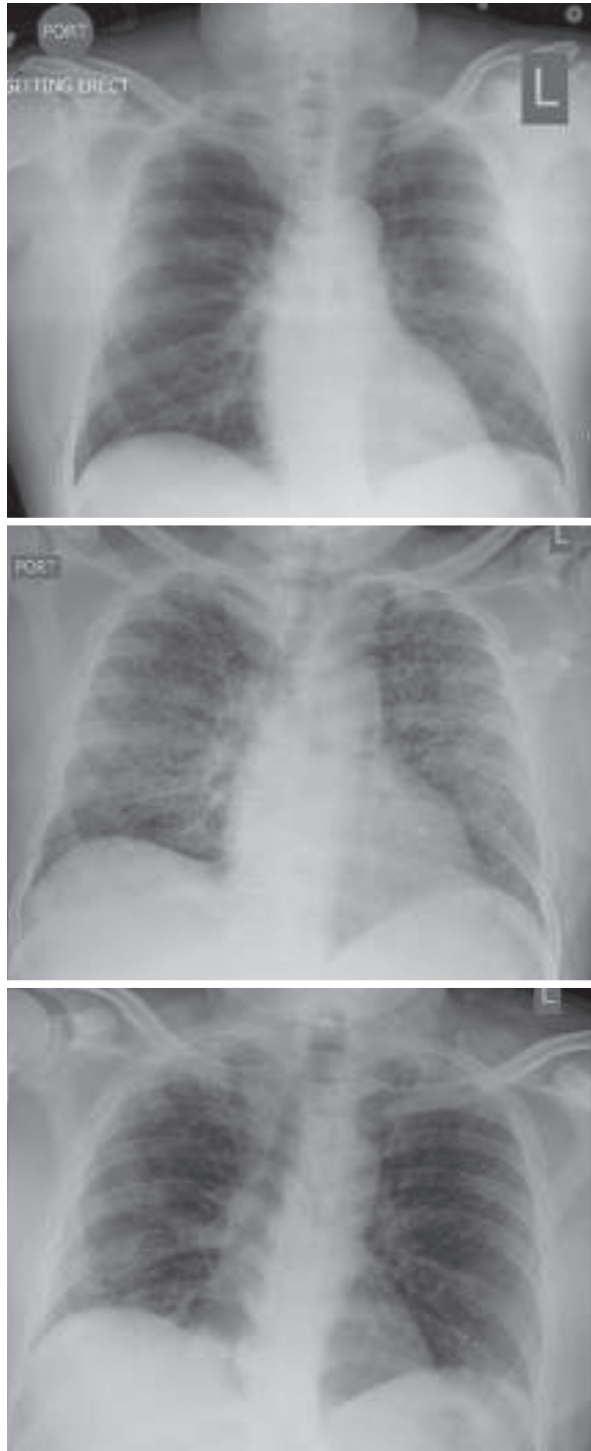


**Figure 15.5** Elderly male with newly diagnosed heart failure and positive for COVID-19 by RT-PCR. Top image shows CT with filling defects within bilateral segmental pulmonary artery branches compatible with pulmonary emboli. There are also bilateral pleural effusions due to congestive heart failure. Bottom image shows the same CT (lung windows) with bilateral lower lobe airspace opacity. In the left lower lobe, a reversed halo lesion is beginning to form with a focal rounded area of ground-glass opacity surrounded by a ring of denser consolidation. Even though this finding is typical of COVID-19 pneumonia, a pulmonary infarct due to pulmonary embolism can have the same appearance.

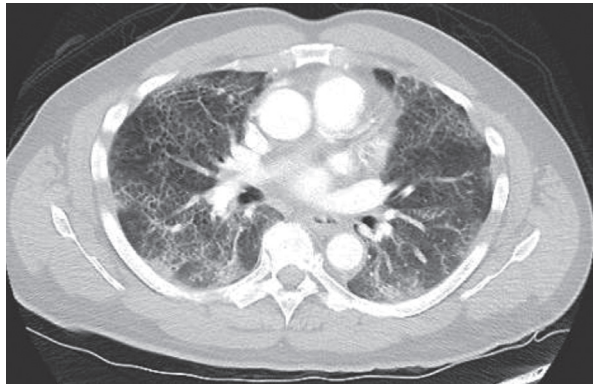




**Figure 15.6** Elderly male presented with fever, myalgia, cough, and shortness of breath and positive for COVID-19 by RT-PCR. Top image shows an initial chest radiograph with minimal ground-glass opacity in the retrocardiac left lower lobe. Middle image shows the follow-up chest radiograph performed 5 days later. There is significantly worse diffuse ground-glass opacity within the bilateral lungs. Bottom image shows a follow-up chest radiograph performed 10 days later on the day of discharge from hospital. There is still ground-glass opacity within the bilateral lungs but it is improved.



**Figure 15.7** Same patient as in Figure 15.5. CT chest performed at time of peak lung disease. There is a crazy-paving pattern of lung disease with thickened interlobular septa and intralobular lines superimposed on a background of ground-glass opacity. This finding is a commonly reported imaging feature of COVID-19 pneumonia.



### 15.3.3 CT Reports

Some organizations have put forth consensus statements to standardize reporting language or CT scoring systems regarding the possibility of COVID-19 pulmonary infection. The Radiological Society of North America (RSNA) proposes dividing reporting language into four classifications for cases where COVID-19 pneumonia is a clinical possibility according to Table 15.2.

Proposed reporting language for CT findings related to COVID-19 includes rationale, CT findings, and suggested reporting language for each category. Suggested reporting language includes coding of CT findings for data mining. Associated CT findings for each category are based upon available literature at the time of writing in March 2020, noting the retrospective nature of many reports, including biases related to patient selection in cohort studies, examination timing, and other potential confounders.

1. Inclusion in a report of items noted in parentheses in the Suggested Reporting Language column may depend upon clinical suspicion, local prevalence, patient status as a UI, and local procedures regarding reporting.
2. CT is not a substitute for RT-PCR; consider testing according to local recommendations and procedures for and availability of RT-PCR.

These classifications are categorized as typical appearance, indeterminate appearance, atypical appearance, and negative for pneumonia. A typical appearance would be peripheral bilateral ground-glass opacity with or without denser consolidation or crazy-paving, multiple rounded ground-glass opacities, or reverse halo sign lesions. An indeterminate appearance would be diffuse, perihilar, or unilateral ground-glass opacity, which is not rounded in appearance and not peripheral in distribution. An atypical appearance would be isolated lobar or segmental consolidation without

ground-glass opacity, numerous small discrete nodules, cavitation, or smooth interlobular septal thickening and pleural effusion. Negative for pneumonia would be no CT findings of pneumonia. Keep in mind that other infectious or noninfectious diseases can have the same appearance as a CT classification of typical appearance for COVID-19 pneumonia and a negative for pneumonia CT does not completely exclude the possibility of COVID-19 pulmonary infection. This leads us to the next topic of the utility of CT chest for diagnosis of COVID-19 pneumonia.

**Table 15.2** Reporting Language Proposed for CT Findings Related to COVID-19

Routine screening CT for diagnosis or exclusion of COVID-19 is currently not recommended by most professional organizations or the US Centers for Disease Control and Prevention			
COVID-19 Pneumonia Imaging Classification	Rationale	CT Findings	Suggested Reporting Language
<i>Typical appearance</i>	Commonly reported imaging features of greater specificity for COVID-19 pneumonia.	<p>Peripheral, bilateral “GGO” with or without consolidation or visible intralobular lines (“crazy-paving”)</p> <p>Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines (crazy-paving)</p> <p>Reverse halo sign or other findings of organizing pneumonia (seen later in the disease)</p>	“Commonly reported imaging features of (COVID-19) pneumonia are present. Other processes such as influenza pneumonia and organizing pneumonia, as can be seen with drug toxicity and connective tissue disease, can cause a similar imaging pattern.” [Cov19Typ] <sup>a</sup>
<i>Indeterminate appearance</i>	Nonspecific imaging features of COVID-19 pneumonia.	<p><i>Absence of typical features AND Presence of:</i> Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are nonrounded or nonperipheral.</p> <p>Few very small GGO with a nonrounded and nonperipheral distribution</p>	“Imaging features can be seen with (COVID-19) pneumonia, though are nonspecific and can occur with a variety of infectious and noninfectious processes.” [Cov19Ind] <sup>a</sup>

**Table 15.2** (continued)

Routine screening CT for diagnosis or exclusion of COVID-19 is currently not recommended by most professional organizations or the US Centers for Disease Control and Prevention			
COVID-19 Pneumonia Imaging Classification	Rationale	CT Findings	Suggested Reporting Language
<i>Atypical appearance</i>	Uncommonly or not reported features of COVID-19 pneumonia.	<i>Absence of typical or indeterminate features AND Presence of:</i> Isolated lobar or segmental consolidation without GGO Discrete small nodules (centrilobular, “tree-in-bud”) Lung cavitation Smooth interlobular septal thickening with pleural effusion	“Imaging features are atypical or uncommonly reported for (COVID-19) pneumonia. Alternative diagnoses should be considered.” [Cov19Aty] <sup>a</sup>
<i>Negative for pneumonia</i>	No features of pneumonia	No CT features to suggest pneumonia.	“No CT findings present to indicate pneumonia. (Note: CT may be negative in the early stages of COVID-19).” [Cov19Neg] <sup>a</sup>

Source: Adapted from:<sup>14</sup>Published online March 25, 2020 © Radiological Society of North America. GGO, ground-glass opacity.

<sup>a</sup>Suggested coding for future data mining.

### 15.3.4 CT Screening

Should CT be used for screening patients for COVID-19 pneumonia? Most radiology organizations do not recommend CT screening routinely to diagnose COVID-19 pneumonia. The Fleischner Society came out with a multinational consensus statement addressing this question.<sup>15</sup> In it, they stated that imaging with CXR or CT is not indicated in patients suspected of having COVID-19 with mild symptoms unless they are at risk for worsening disease, imaging is indicated in patients who have COVID-19 pneumonia and worsening respiratory status, and in a resource-constrained environment, imaging is indicated to triage patients with moderate to severe clinical features who have a high pretest probability of COVID-19 pneumonia. In their statement, the Fleischner Society did not specify in these recommendations whether the imaging modality to be used should be CXR or CT as this would

be based upon local resources and expertise. Although CT is better for detecting early or mild pneumonia and alternative diagnoses, it is significantly more expensive, more time-consuming, and involves a greater radiation dose.

### 15.3.5 CT Protocol

Chest CT volume reconstructions at 0.625–1.5 mm slice thickness ideally evaluate interstitial lung disease. Intravenous contrast is not required except in cases where the vasculature needs to be evaluated such as CT pulmonary angiography for the evaluation of pulmonary embolism.

## 15.4 Ultrasound

Lung ultrasound has advantages in that it is low cost, does not use ionizing radiation, and can be done portably at the bedside which is particularly helpful in the emergency department or intensive care unit setting. Findings seen on lung ultrasound in COVID-19 pneumonia include B-lines, consolidative pattern, thickened pleural lines, and A lines during the recovery phase.<sup>16, 17</sup>

The World Health Organization (WHO) recently published a guide on imaging in COVID-19 in which they stated that although lung ultrasound has very low-certainty evidence supporting its diagnostic accuracy, it might be helpful with the appropriate expertise as a supplemental or alternative imaging modality particularly in pregnant women, children, and patients who are mechanically ventilated.<sup>18</sup>

## 15.5 Magnetic Resonance Imaging (MRI)

While CT utilizes X-rays, MRI uses strong magnetic fields and radio waves to produce its images, utilizing the signal obtained from the relaxation of protons within the body. While CT is more available, less expensive, and is a much quicker examination to perform, MRI can provide greater sensitivity for pathology in many cases depending on the organ and what disease is being evaluated for. The strong magnetic fields used in MRI may preclude imaging of patients who have certain ferromagnetic medical devices such as pacemakers although more and more medical devices, including some pacemakers, are becoming MRI compatible.

The clinical utility of MRI for evaluating the lungs is limited. Because the lungs are full of air, and are therefore relatively proton-deficient, MRI has a limited sensitivity for pulmonary pathology. Air additionally results in bulk susceptibility artifacts on MRI, limiting visualization of anatomy in and around structures that contain air. One of the clinical roles for MRI in evaluating the chest is evaluating for cardiac myocarditis.

The Journal of the American College of Cardiology (JACC) scientific expert panel has updated consensus recommendations for cardiovascular magnetic resonance (CMR) diagnosis of myocardial inflammation in patients suspected of having acute or active myocardial inflammation in 2018.<sup>19</sup> These updated criteria, referred to as the updated Lake Louise Criteria II, are evaluating for myocardial edema and inflammation, and require abnormality on both T2-based and T1-based magnetic resonance imaging with supportive criteria, including the presence of a pericardial effusion or signs of pericarditis and cardiac left ventricular systolic wall motion abnormality. The administration of MRI gadolinium-based intravenous contrast during the examination, to evaluate for late enhancement of the myocardium in a nonischemic pattern, is helpful to make the diagnosis but is not absolutely necessary.

One study from Germany evaluated the presence of myocardial injury on CMR in 100 patients recently recovered from COVID-19 infection.<sup>20</sup> This study showed that there was cardiac involvement in 78% of patients with ongoing myocardial inflammation in 60% of patients independent of preexisting conditions, severity and length of acute illness, time from original diagnosis, or the presence of cardiac symptoms.

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## List of Abbreviations

ARDS	Acute respiratory distress syndrome
CBC	Complete blood count
CPK	Creatine phosphokinase
CRP	C-reactive protein
CXR	Chest X-ray
ESR	Erythrocyte sedimentation rate
HAPE	High-altitude pulmonary edema
HFNC	High-flow nasal cannula
HLH	Hemophagocytic lymphohistiocytosis
ICU	Intensive care unit
LFT	Liver function test
LTVV	Low tidal volume ventilation
MAP	Mean arterial pressure
NIPPV	Noninvasive positive pressure ventilation
PBW	Predicted body weight
PEEP	Positive end-expiratory pressure
PPE	Personal protective equipment
VV ECMO	Veno-venous extracorporeal membrane oxygenation

## 16.1 Introduction

The epidemiology, etiology, diagnosis, and management of severe COVID-19 patients will be discussed in this chapter. The main focus of this chapter is on the management of hypoxemic respiratory failure in the intubated and nonintubated patient. Special considerations in management, including the role of anticoagulation and corticosteroids in COVID-19 patients, will also be discussed.



## 16.2 Epidemiology

In 20% of cases, COVID-19 can become severe very quickly and some patients rapidly deteriorate 1 week after the start of symptoms. Severe COVID-19 is characterized by worsening dyspnea, hypoxia, or greater than 50% lung involvement on imaging within 24–48 h of presenting symptoms.

Wu et al. reported that 14% of COVID-19 patients have severe disease (hypoxemia or greater than 50% lung involvement on imaging) and approximately 5% have critical disease (respiratory failure, multiorgan failure, and/or shock).<sup>1</sup> Among those with critical disease, case fatality rate was reported to be 49%. Among patients who develop severe disease, the mean duration to develop dyspnea was 5–8 days; acute respiratory distress syndrome (ARDS) was 8–12 days; and intensive care unit (ICU) admission was 10–12 days.<sup>2,3</sup>

Hypoxemic respiratory failure is the most common reason patients with COVID-19 are admitted to the ICU.<sup>4</sup> Mortality among patients admitted to the ICU has been reported to be between 39 and 72%. Of critically ill patients, 71% need mechanical ventilation, often requiring extended mechanical ventilation with a median time to extubation of 11–17 days.<sup>5</sup> About 70% eventually require vasopressors and 33% will develop cardiomyopathy.<sup>6</sup> Increased age, comorbidities (diabetes, hypertension, coronary artery disease, malignancy, and chronic lung disease), and laboratory abnormalities have been associated with disease severity.

In addition to provider concern, high nursing requirements, and risk of decompensation from severe comorbid illness, consideration for transfer or admission to the ICU includes signs of respiratory distress (rapid increase in oxygen requirement, high work of breathing, oxygen need greater than 6 liters per minute (LPM)), hemodynamic instability, acidosis (pH <7.3), and high levels of lactate (>2). If the decision is made to transfer to the ICU, hospital policy for transfer and personal protective equipment (PPE) must be followed to minimize the risk of transmission to health-care workers.

## 16.3 Initial Testing and Imaging

For most ICU patients, the COVID-19 nasal swab and comprehensive respiratory panel testing would have already been collected in the emergency department. If not, this will need to be done once admitted to the ICU. Additional laboratory testing that will need to be drawn on patients with severe COVID-19 includes chemistry panel and liver function tests (LFTs), including albumin, complete blood count (CBC) with differential, procalcitonin, ferritin, triglycerides, fibrinogen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), troponin, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), D-dimer, and prothrombin time (PT).<sup>7</sup> Most of these laboratories are regularly repeated throughout the patient's ICU stay because they have been found to be markers that may track the disease severity and prognosis (Table 16.1). Troponin as well as an electrocardiogram (ECG or EKG) is used to assess for cardiomyopathy and conduction disturbances in a deteriorating

**Table 16.1** Laboratory Markers Associated with Severe COVID-19 Diagnosis

Laboratories associated with severe disease	
CBC	
WBC	>10 K/uL
Lymphopenia	<1.00 K/uL
Platelets	<150 K/uL
CPK	>185 U/L
Creatinine	>1.5 mg/dL
D-Dimer	>1000 ng/mL
Ferritin	>300 ug/L
High-sensitive cardiac troponin-T	>~20 ng/L
IL-6	>10 pg/mL
LDK	>245 U/L
LFTs	
Albumin	<3 g/dL
ALT	>40 U/L
Procalcitonin	>0.5 ng/mL

patient. Higher-than-expected cardiovascular deaths (VT/VF, asystole) have been seen in COVID-19 patients. A small subgroup of severe ICU patients develop secondary hemophagocytic lymphohistiocytosis (HLH)<sup>8</sup> and acute pulmonary embolism.<sup>9</sup>

As for imaging, portable chest X-rays (CXRs) are sufficient in most cases for assessing the patient's lung parenchyma.<sup>10</sup> The most common CXR finding is bilateral patchy infiltrates which may evolve rapidly.<sup>11</sup> Routine chest CT increases the risk of viral transmission to health-care workers and has a low specificity as a screening tool.<sup>12,13</sup> It is generally not recommended by the American College of Radiology.<sup>14</sup> On CT scan, COVID-19 pneumonia was similar to a viral pneumonia, but was more likely to have ground-glass opacifications, vascular thickening, and fine reticular opacities.<sup>15</sup> However, early in the course of the disease, a normal chest CT does not exclude COVID-19 and an abnormal CT scan cannot diagnose COVID-19. Therefore, CT scanning is limited to patients who clinically show symptoms of a complication such as an empyema or abscess or concern of pulmonary embolism.

Additionally, bronchoscopy is not recommended or necessary for the purpose of ruling COVID-19 in or out and should be avoided to minimize aerosolization and increasing transmission. Bronchoscopy should only be done if it will change clinical management and should be completed in a negative pressure room, if at all possible.

**Table 16.2** The Berlin Criteria for ARDS

Berlin Criteria for ARDS <sup>16</sup>	
Acute onset of 1 week or less	
Bilateral opacities on chest CT or CXR	
Must not be fully explained by cardiac failure or failure overload	
Oxygenation	
Mild	PaO <sub>2</sub> /FiO <sub>2</sub> > 200 mmHg but ≤ 300 mmHg PEEP or CPAP ≥5 cm H <sub>2</sub> O
Moderate	PaO <sub>2</sub> /FiO <sub>2</sub> > 100 mmHg but ≤ 200 mmHg PEEP ≥5 cm H <sub>2</sub> O
Severe	PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 100 mmHg PEEP ≥5 cm H <sub>2</sub> O

## 16.4 Etiology of Hypoxemic Respiratory Failure in COVID-19

In the media, there has been discussion about whether hypoxemic respiratory failure from COVID-19 is ARDS, another process similar to high-altitude pulmonary edema (HAPE), or some other novel syndrome. Since ARDS is not a specific disease, but rather a clinical syndrome with varying disease severity, COVID-19 fits the spectrum of ARDS as defined by the Berlin criteria (Table 16.2).<sup>7</sup>

The noncardiogenic pulmonary edema (edema that develops in the setting of normal left atrial pressures) resulting from HAPE, ARDS from COVID-19, and many other causes is due to an imbalance in Starling forces. The reasons for the imbalance are markedly different between ARDS and HAPE. In ARDS from COVID-19 or other causes, inflammation and the innate immune response leads to damage of the alveolar epithelium and endothelium and increased capillary permeability, leading to fluid accumulation in both alveolar spaces and interstitium. Proinflammatory cytokines, secreted by alveolar macrophages, sustain inflammation and lung injury leading to ventilation–perfusion mismatch and hypoxemia. On the other hand, the noncardiogenic pulmonary edema that results from HAPE is due to excessive hypoxemic pulmonary vasoconstriction, and not an inflammatory process. Therefore, treating COVID-19 with medications used to manage HAPE is unlikely to be beneficial and may be harmful.

## 16.5 Management of Hypoxemia in Nonintubated Patients

Case series from Seattle, China, and Italy suggest a range of disease severity, gas exchange impairments, and respiratory compliance.<sup>2, 3, 17, 18</sup> For the management of hypoxemia in nonintubated individuals, nasal cannula up to 6 LPM should be the first-line treatment to meet oxygenation goals (eg, oxygen saturation 90–96%). If not sufficient, a nasal pendant can be used up to 12 L or a non-rebreather up to 15 L should be used to titrate SpO<sub>2</sub> saturation to greater than 90%.

Self-proning (spending as much time as is feasible and safe in the prone position while receiving oxygen) may improve the recruitment of alveoli in dependent areas of the lung and may improve perfusion to ventilated areas, thus improving V/Q mismatching in nonintubated patients.<sup>19</sup> Proning is used in ventilated patients, and while low tidal volumes cannot be guaranteed in spontaneously breathing patients, self-proning in nonintubated patients is likely safe and is being used at some institutions.<sup>20, 21</sup>

There are conflicting opinions about using noninvasive ventilation and high-flow nasal cannulas (HFNCs) to extend the time before a patient becomes intubated. In patients who are suffering from ARDS, studies show a frequent need for mechanical ventilation despite the use of these measures. Another significant consideration is that both interventions aerosolize the virus, risking infecting the staff and further increasing transmission. Both the WHO and SCCM guidelines make weak recommendations for HFNC in select patients.<sup>22</sup>

## 16.6 Management of Intubated Patients

Early controlled elective intubation is recommended if there is (1) a rapid progression over hours; (2) persistent or worsening hypoxemia despite nasal pendant or non-rebreather; (3) hypercapnia, accessory muscle use, and altered mental status; and/or (4) hemodynamic stability or multiorgan failure. Since intubation is a high-risk procedure for droplet dispersion, airborne PPE should be used and the procedures should be performed in an airborne infection isolation room if possible.

Since COVID-19-associated respiratory failure fits the spectrum of ARDS, evidence-based management of ARDS should be applied to COVID-19-associated respiratory failure. The principles of ARDS management include lung protective ventilation (low tidal volume ventilation, LTVV),<sup>23</sup> positive end-expiratory pressure (PEEP) titration, conservative fluid management, and prone ventilation.

### 16.6.1 Lung Protective Ventilation

The initial ventilator settings should use the volume-assisted control to achieve LTVV [4–8 cc/kg of predicted body weight (PBW), targeting a plateau pressure (P<sub>plat</sub>) ≤30 cm H<sub>2</sub>O]. LTTV, adjusted by PBW and thereby lung size, can minimize volutrauma (overdistension of already-open alveoli). This approach is based on several RCTs showing an improved mortality from LTVV in patients with ARDS.<sup>24</sup>

### 16.6.2 PEEP Titration

Titrating PEEP can prevent decruitment, thereby increasing functional lung size and decreasing the risk of volutrauma. PEEP and FiO<sub>2</sub> are titrated to target oxygenation (goal: SpO<sub>2</sub> 92–96%) per the ARDS net low PEEP (Table 16.3).<sup>7</sup> Patients are

**Table 16.3** PEEP and FiO<sub>2</sub> Levels and ARDS

Low PEEP ARDS Net Table	
FiO <sub>2</sub>	PEEP
0.3	5
0.4	5
0.5	8
0.6	10
0.7	10–14
0.8	14
0.9	14–18
1	18–24

sometimes started on higher-than-usual levels of PEEP (10–15 cm H<sub>2</sub>O) since reports suggest that some COVID-19 ARDS patients are responsive to high PEEP and have high lung compliance such that P<sub>plat</sub> ≤30 cm H<sub>2</sub>O is not difficult to achieve.

### 16.6.3 Conservative Fluid Management

A conservative fluid approach is one of the mainstays of ARDS management.<sup>25</sup> ARDS is a form of noncardiogenic pulmonary edema due to increased capillary permeability,<sup>26</sup> which can be worsened by an increase in hydrostatic forces. The Fluid and Catheter Treatment trial showed that conservative fluid management can improve oxygenation, ventilation-free days, and lung injury.<sup>27</sup> Reducing intravascular volume to reduce pulmonary edema needs to be balanced with the need for adequate perfusion to nonpulmonary organs. In practical terms, this translated to avoiding a positive fluid balance (sometimes requiring the administration of diuretics) in patients post-resuscitation and without ongoing shock.

### 16.6.4 Prone Ventilation

Prone ventilation is the delivery of mechanical ventilation with the patient in the prone position and is a key component of management of patients with severe ARDS who are intubated. Studies have demonstrated improved oxygenation, and one study showed a mortality benefit with ventilation in the prone position in those with severe ARDS.<sup>28–30</sup> Prone positioning is recommended for patients with severe ARDS whose P/F remains less than 150 mmHg for 12 h despite ventilator optimization with LTVV in the supine position. Prone positioning is usually implemented early in the course of ARDS (within 36 h), and patients are usually maintained in the prone position for 16–18 consecutive hours per 24 h. For patients who have a

sustained improvement in gas exchange, prone positioning is usually stopped when improvement in oxygenation ( $P/F \geq 150$  mmHg,  $FiO_2 \leq 0.6$ ,  $PEEP \leq 10$  cm H<sub>2</sub>O,  $Ppl < 30$ ,  $pH > 7.25$ ) is maintained for at least 4 h after the end of the last prone session. If prone ventilation fails, the patient should be returned to the supine position.

Absolute contraindications to prone positioning include spinal instability or at risk for spinal instability, unstable fractures, shock, anterior burns and open wounds, recent tracheal surgery, pregnancy, and raised intracranial pressure. Other contraindications include abdominal surgery, hemodynamic instability, and life-sustaining cardiac hardware. Common complications include transient desaturations, facial and ocular edema, decubitus ulcers, and dislodgement of catheters and endotracheal tubes.

### 16.6.5 Inhaled Pulmonary Vasodilators

Inhaled nitric oxide (iNO), a rapid acting vasodilator, selectively vasodilates the already well-ventilated areas, improving V/Q mismatch.<sup>31</sup> A systematic review showed an improvement in P/F ratios at 24 h, but not at 48 or 72 h with iNO. There were no differences in duration of mechanical ventilation and length of ICU stay, but a significant increase in renal failure in the iNO group.<sup>32</sup> There has been one small study in Beijing during the SARS epidemic, showing that iNO improved oxygenation and decreased the amount of days on the ventilator.<sup>33</sup> iNO may also have direct antiviral effects.<sup>34–36</sup> iNO or other pulmonary vasodilators like nebulized epoprostenol (a synthetic analogue of prostacyclin) may therefore have a role as rescue therapy in some patients with COVID-19 who have persistent hypoxemia that is unresponsive to PEEP titration and prone ventilation.

### 16.6.6 Venovenous Extracorporeal Membrane Oxygenation (VV ECMO)

VV ECMO is a type of pulmonary bypass allowing oxygenation to occur via an external membrane. Studies suggest that in severe ARDS, ECMO could be used after the failure of optimized ARDS management. Specifically, ECMO can be considered when there are no reversible causes and P/F is persistently  $< 75$  mmHG despite optimized PEEP, neuromuscular blockade, proning, and inhaled vasodilator;  $Ppl > 30$  cm H<sub>2</sub>O despite lung protective ventilation; and  $pH < 7.2$ . Some studies suggest that referral to ECMO centers should be made early (within 7 days of severe ARDS).<sup>37</sup> Absolute and relative contraindications to ECMO include advanced age, active malignancy, severe shock, multiorgan failure, severe neurologic injury, poor functional status, inability to anticoagulate, high body mass index ( $> 40$ ), thrombocytopenia (platelets less than 50), and neutropenia (absolute neutrophil count (ANC)  $< 500$ ). In the Extracorporeal Life Support Organization algorithm, there are no absolute contraindications except for end-stage respiratory failure when lung transplantation is not an option. Thromboembolism and bleeding are the major complications from ECMO.

## 16.7 Sedation/Analgesics/Paralytics

Prior studies show that lower levels of sedation and nonbenzodiazepine regimens decrease ICU days and duration of mechanical ventilation.<sup>38</sup> To achieve appropriate sedation and analgesia, the lowest dose of any medication should be used to achieve the desired effect. Ventilation synchrony is very important to help reduce ventilator-induced lung injury, and this is achieved by appropriately balancing the sedative, analgesic, and neuromuscular blockade agents.<sup>7</sup> The Richmond Agitation-Sedation Scale, a validated 10-point scale (−5 to +4) to assess a patient's level of sedation in the ICU, can be used to help describe the level of alertness or agitation in mechanically ventilated patients to prevent over- or under-sedation.<sup>39</sup> The target score is 0 to −1 to maintain synchrony, without agitation (2–4), or over-sedation (−3 to −5).

The preferred therapy for sedation in many centers is propofol so as to avoid the use of benzodiazepines, particularly for patients with ARDS who have renal and/or liver dysfunction. Several cases of propofol-associated triglycerides and pancreatitis have been reported.<sup>40</sup> Although reported in less than 1% of patients, propofol infusion syndrome should be considered in patients receiving either high dose (>5 mg/kg/h) or longer duration (>48 h) who have unexplained metabolic acidosis, rhabdomyolysis, and EKG changes, with or without acute kidney injury, cardiac failure, or higher levels of liver enzymes, lactate, lipids, or potassium. Midazolam is often the second-line therapy for sedation.<sup>41</sup> Obese patients are at an increased risk for prolonged sedation given the accumulation of drug and metabolite in excess adipose tissue. A slow and steady decrease in the rate of infusion can facilitate weaning without precipitating a withdrawal syndrome. Since dexmedetomidine is unlikely to provide deep levels of sedation, in the current climate it is often used as an adjunct to other sedatives, or as a 24- to 48-h bridge to wean benzodiazepines to facilitate extubation.

For analgesia in intubated patients, the first-line therapy is fentanyl or hydromorphone because these agents are fast-acting and titratable.<sup>7</sup> Fentanyl is typically given as a continuous infusion. Since fentanyl is highly lipophilic, accumulation in fat and other tissues can result in prolonged sedation even after discontinuation. Hydromorphone is an alternative to fentanyl with dosing adjusted for hepatic or renal insufficiency.<sup>7</sup> Because of its longer duration of action, hydromorphone is preferred if patients only require intermittent bolus dosing.

A subset of patients with severe ARDS ( $\text{PaO}_2:\text{FiO}_2 < 150$  after at least 12 h of mechanical ventilation using  $\text{FiO}_2 > 0.6$  and  $\text{PEEP} > 5$  cm H<sub>2</sub>O) and ventilator dys-synchrony causing high plateau pressures (>30cm H<sub>2</sub>O) or injurious tidal volumes ( $\text{TV} > 8$  cc/kg IBW) or hypoxemia may benefit from neuromuscular blockade. Since neuromuscular blockade therapies do not have any analgesic or sedative properties, deep sedation is necessary before neuromuscular blockade is initiated. Cisatracurium is often used as a first-line treatment and preferred in patients who have renal and liver dysfunction as well as hemodynamically unstable patients. Alternative agents include vecuronium, rocuronium, and atracurium.<sup>7</sup>

## 16.8 Weaning and Extubation

There is extensive literature on liberation from mechanical ventilation.<sup>42</sup> Guidelines for consideration of a weaning trial include (1) ability to initiate own breaths, (2) resolution of the underlying disease process, (3) improved gas exchange (eg, O<sub>2</sub> saturation >90% on 40% oxygen or less, or PaO<sub>2</sub>/FiO<sub>2</sub> >150), (4) minute ventilation requirements not excessive (eg, less than 12 L/minute; RR < 30), (5) preserved mental status, (6) lack of excessive pulmonary secretions, and (7) hemodynamic stability.

Once these criteria have been met, daily spontaneous breathing trials (SBT) remain the most effective method to wean from mechanical ventilation.<sup>43–45</sup> An SBT consists of a trial on minimal PEEP (5 cm H<sub>2</sub>O) and pressure support (usually 0–5 cm H<sub>2</sub>O) for a set period of time (30–120 min). The patient should be assessed for the following respiratory parameters: SpO<sub>2</sub> >90 and/or PaO<sub>2</sub> > 60 mmHg, spontaneous tidal volume 4–6 ml/kg PBW, respiratory rate less than 35 per min, pH > 7.3, and no signs of respiratory distress. Once the patient can tolerate the SBT for 30–120 min while remaining hemodynamically stable with noncopious secretions and sufficient mental status, extubation can be considered.<sup>46</sup>

Prior to extubation, glucocorticoids should be considered due to evidence of preventing stridor, laryngeal edema, and reducing the incidence of reintubation.<sup>47–49</sup> Therefore, 40 mg of methylprednisolone IV should be given 4–6 h prior to planned extubation, with a maximum dose of 80 mg if extubation is delayed. Patients who have passed an SBT and are considered at high risk for postextubation respiratory failure (age >65, CHF, COPD, hypercapnia during SBT) had improved outcomes with noninvasive positive pressure ventilation (NIPPV) or HFNC in the immediate postextubation period.<sup>50–52</sup> Alternatively for patients who develop respiratory failure within 48 h of extubation, NIPPV as a rescue therapy for respiratory failure has been shown in some studies to increase all-cause mortality.<sup>53</sup>

Since intubation, reintubation, NIPPV, and HFNC are considered aerosol-generating procedures, the following modifications should be considered in COVID-19 patients:

- Consider extending SBT trials to 2 h to ensure higher likelihood of postextubation failure.
- Consider an SBT trial with no additional PEEP to ensure patients can tolerate no PEEP postextubation.
- Carefully consider the risk to health-care workers and review hospital policy prior to using NIPPV and HFNC postextubation in COVID-19 patients that have passed an SBT trial but are at high risk for postextubation failure.

## 16.9 Tracheostomy

Since tracheostomy is an aerosol-generating procedure and increases potential viral exposure to the health-care team, decision-making in tracheostomy should take into account the surgical team and hospital policy. The American Academy of



Otolaryngology-Head and Neck Surgery has issued guidelines on tracheostomy during the COVID-19 pandemic.

### 16.9.1 Tracheostomy Recommendations during the COVID-19 Pandemic

At the time of this writing, there is no data on the role of tracheostomy in COVID-19 patients. Tracheostomy can be considered in patients with stable respiratory status but not sooner than 2–3 from intubation. Overall, early tracheostomy placement (earlier than 10 days) is not recommended due to previous studies showing no improvement in survival, ventilator-associated pneumonia rate, or duration of mechanical ventilation for patients with respiratory failure.<sup>54</sup> It is important to note that the average duration of ventilation in COVID-19 patients is about 8 days and the average ICU stay is around 10 days. Therefore, there is minimal evidence to support early tracheostomy placements in COVID-19 patients, even if early tracheostomies were to reduce health-care resources. Patients who have a tracheostomy placed need long-term care, and this needs to also be considered when thinking of placing early tracheostomies in patients who might be able to be extubated prior to needing a tracheostomy.<sup>55</sup>

## 16.10 Cytokine Storm

It has been postulated that a subgroup of patients with severe COVID-19 exhibit a dysregulated immune response, or “cytokine storm” that leads to progressive disease.<sup>56</sup> The “cytokine storm” appears to be similar to the hyperinflammation seen in other virally triggered secondary HLH. In HLH, aggressive immune activation of macrophages leads to an excessive cytokine response with both laboratory and clinical evidence of severe inflammation.<sup>57</sup> This immune activation increases ferritin, ESR, and CRP; decreases platelets; and can lead to worsening respiratory failure and multiorgan failure.

It is unclear if immunosuppression in this subset of patients with severe inflammation can improve mortality. IL-6 activates T cells and macrophages, and increased levels of IL-6 may be associated with COVID-19 disease severity,<sup>58, 59</sup> but it is unclear if blocking this cytokine could lead to improved clinical outcomes. IL-1 is a proinflammatory cytokine elevated in critical illness. Modulation of cytokines with monoclonal antibodies such as tocilizumab and sarilumab (monoclonal antibodies against the IL-6 receptor) and anakinra (recombinant antagonist of the IL-1 receptor) is being studied in clinical trials. Trials are additionally underway to test whether treatment with etoposide (by eliminating the cells that are causing the excessive cytokine response) improves clinical outcomes.<sup>7</sup> The Hscore may be useful in identifying patients with HLH who should be considered for clinical trials.<sup>60</sup> This score calculates the probability of HLH by assessing characteristics such as underlying immunosuppression, temperature, hepatomegaly or splenomegaly,

number of cytopenias, ferritin levels, triglyceride and fibrinogen levels, AST as well as if there are hemophagocytosis features on bone marrow aspirate.<sup>61</sup>

## 16.11 Shock Management

While patients rarely present with shock (MAP <65 or SBP < 90 with signs of hypoperfusion requiring IVF or vasopressors to maintain adequate blood pressure), vasopressors are eventually used in about 70% of critically ill patients. The reason for shock in patients with COVID-19 is most often secondary to bacterial infection, cardiac dysfunction, or cytokine storm.<sup>7</sup> The workup for shock should include assessing for end-organ damage (altered mental status; decreased urine output; abnormal electrolytes; and high levels of lactate, LFTs, and BUN/creatinine) and obtaining an infectious and cardiac workup. One study reported that 20% of COVID-19 nonsurvivors had a secondary bacterial infection and that 52% of nonsurvivors had heart failure or cardiogenic shock, usually presenting later in the disease course.<sup>62</sup>

Management of septic shock should include early antibiotics and maintaining MAP above 65 mmHg. Since the majority of ICU patients with COVID-19 have ARDS, a more conservative fluid strategy is preferred over the conventional fluid strategy of 30 cc/kg to avoid exacerbating ARDS. Therefore, 250–500 cc of fluid should be given and the patient assessed for an increase in MAP or decrease in pressor requirements in 15–30 min. 250–500 cc of fluid can be repeated. If pressors are needed, norepinephrine is the initial vasopressor of choice (1–30 mcg/min).<sup>7</sup> If a second vasopressor is needed, vasopressin of 0.4 units can be used. Cardiogenic shock should be comanaged with the cardiology team. Routine monitoring should include troponin, lactate, LFTs, SCvO<sub>2</sub> or MvO<sub>2</sub>, and daily EKGs. Achieving a mean arterial pressure (MAP) of greater than 65 may require a combination of vasopressors (norepinephrine), diuretics, and inotropic support (dobutamine).

## 16.12 Anticoagulation in COVID-19 Patients

D-dimer, a marker associated with thrombosis, is often increased in patients with severe COVID-19, and several studies have shown high rates of thrombotic events in patients with severe COVID-19.<sup>63–66</sup> In addition, ARDS of itself is known to be associated with coagulopathy and both macrovascular and microvascular thrombosis. Yet no clinical trials have demonstrated a benefit from therapeutic anticoagulation in patients with ARDS.<sup>67</sup> Although ARDS and COVID-19 are associated with hypercoagulable states, there is a limited evidence that therapeutic anticoagulation improves outcomes.

Since critically ill patients with COVID-19 have a high rate of thrombosis (23–43% in ICU patients), prophylactic anticoagulation is imperative for critically ill patients, unless contraindicated. Low molecular weight heparin is preferred, but unfractionated heparin is used if kidney function is impaired (creatinine clearance

<30 ml/min). Some institutions use more aggressive anticoagulation with intermediate-dose anticoagulation for prophylaxis in patients with very high D-dimer levels. Therapeutic dose anticoagulation is used to treat deep vein thrombosis or pulmonary embolism, unless contraindicated.

### 16.13 Corticosteroids in COVID-19 Patients

Preliminary data from the RECOVERY trial, a randomized trial of >6000 hospitalized patients with COVID-19, demonstrates that dexamethasone has a mortality benefit in patients with COVID-19 who require oxygen or are mechanically ventilated.<sup>68</sup> Patients who did not require oxygen did not benefit from dexamethasone. Therefore, for patients with COVID-19 on supplemental oxygen (whether spontaneously breathing or mechanically ventilated), dexamethasone 6 mg either intravenously or by mouth for 10 days (the equivalent of 40 mg prednisone daily) should strongly be considered if not contraindicated.

### 16.14 Palliative Care

In the ICU setting, palliative care consult services have an increasingly important role in helping medical teams with goals of care and advanced care planning discussions with patients and health-care proxies. For patients who are end-of-life, palliative care services also provide support and guidance in symptom management, particularly with opioids and benzodiazepines to help control pain and anxiety. Some hospitals, like the Brigham and Women's Hospital, implemented COVID-19 Intensive Palliative Care Units during the pandemic to help provide support and comfort-focused care to COVID-19 patients with organ failure and an estimated prognosis of less than 1 week.<sup>7</sup>

Consultations with palliative care should happen early so that a plan is set in place that is in accordance with patients' wishes. These discussions are particularly important since cardiopulmonary resuscitation may not offer a benefit in some patients with COVID-19, particularly those with advanced age (>80 years old) and/or comorbid cardiovascular disease, hypertension, diabetes, and respiratory disease and increase transmission to health-care workers. Several resources are available to help providers initiate and respond to often very difficult conversations.

- Center to advance palliative care
- VITAL talk.

### 16.15 Conclusion

- COVID-19 can become severe very quickly, and transfer or admission to ICU should be considered with any of the following: provider concern, high nursing requirements, risk of decompensation from severe comorbid illness, signs of

respiratory distress, hemodynamic instability, acidosis, and increased levels of lactate (>2).

- Evidence-based management of ARDS, including lung protective ventilation (LTVV), PEEP titration, conservative fluid management, and prone ventilation, should be applied to COVID-19-associated respiratory failure.
- Prophylactic anticoagulation is imperative for critically ill patients, unless contraindicated, with some institutions using more aggressive anticoagulation with intermediate-dose anticoagulation for prophylaxis in patients with very high D-dimer levels.
- If not contraindicated, patients with COVID-19 should be considered for corticosteroids if they require supplemental oxygen (whether spontaneously breathing or mechanically ventilated).

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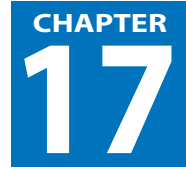
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# Post-Recovery and Long-Term Complications



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## List of Abbreviations

ARDS	Acute respiratory distress syndrome
CNS	Central nervous system
COVID-19	Coronavirus disease
DLCO	Carbon monoxide diffusion capacity
FVC	Forced vital capacity
HRQoL	Health-related quality of life
MERS	Middle East respiratory syndrome
PNS	Peripheral nervous system
SARS	Severe acute respiratory syndrome
TLC	Total lung capacity

## 17.1 Introduction

Coronavirus disease (COVID-19) is a new disease, with the first positive cases emerging in December 2019; there are no studies about its long-term impact on health, especially in people with severe symptoms. The evidence from earlier chapters suggests that SARS-CoV-2 can attach to, and penetrate, human cells in many parts of the body, including many major organs such as the lungs, heart, kidneys, brains, and even blood vessels. Although it may be too early to know of longer-term complications of COVID-19, this chapter will discuss what has been learned about the pathophysiologies and long-term complications seen in the cases of the other two coronaviruses, Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), and compare potential similarities with COVID-19.<sup>1</sup>

## 17.2 SARS—Post-Recovery and Long-Term Complications

The literature assessing long-term complications of SARS is now available given the long follow-up time (18 years), and allows for more complete analysis and understanding of the aftermath associated with this first 2003 coronavirus epidemic.



In order to better discuss the health results from SARS, post-recovery will be defined as symptomology and complications associated with SARS within a 1-year span of disease recovery. Long-term complications will be defined as any disease symptomology or complications that persist or emerge 1 year following recovery.

In regard to the post-recovery phase of SARS, respiratory complications were seen to persist in people over 60 years who experienced severe symptoms.<sup>2</sup> In 15 out of the 24 patients (62%), who underwent computerized tomography (CT) of the thorax 5 weeks post-hospitalization, showed changes associated with pulmonary fibrosis in 62% of patients but a mild decrease in total lung capacity (TLC) 81% of predicted and forced vital capacity (FVC). In these patients, the residual volume was at 65% of predicted. In the post-recovery phase, 6–20% of SARS patients were found to have a mild to moderate muscle weakness.<sup>2</sup>

Another data series in the same study evaluated the health impact that SARS had on 258 patients from Xiaotangshan Hospital in Beijing. It was reported that 2 months post-hospitalization, 21% (54 individuals) had impaired carbon monoxide diffusion, while 6% (16) had a restrictive ventilatory defect FVC.<sup>2</sup> After an additional month, the carbon monoxide diffusion capacity (DLCO) improved in 80.3% of those 54 patients and 81.3% of those 16 patients had an improved FVC. The authors concluded that while most patients affected by SARS made a complete recovery after 3 months post-discharge, there were a small percentage of people that continued to have persisting respiratory problems.

The long-lasting effects of SARS in some patients were confirmed by another study from Hong Kong that evaluated SARS patients at 6 months and 1 year after infection.<sup>3</sup> At 6 months, the researchers found that 33 (30%) of patients presented with abnormal chest radiographs, and 4, 7, and 16% of patients had FVC, TLC, and DLCO below 80% predicted, respectively. At 1-year follow-up, 27 (28%) had abnormal chest radiographs. 4, 5, and 23% of patients had FVC, TLC, and DLCO below 80% predicted, respectively. The study shows that while active recovery takes place within the first couple months post-hospitalization, the overall number of individuals who make a complete recovery from the SARS infection tapers off with a small subset of patients continuing to experience respiratory difficulties.

SARS studies of longer-term lung function at 12 and 15 years post-infection further reveal that while most patients did make a full recovery, a small subset continued to experience permanent lung-related damage.<sup>4,5</sup> It is important to note that all subjects were normal on the basis of a clinical evaluation at the 12-year mark, and only a more in-depth examination revealed persistent lung injury.

Outside of respiratory concerns, additional long-term complications included muscle weakness, chronic fatigue, depression, nonrestorative sleep, and bone problems prominently among patients. A study of 22 SARS patients in Toronto who were followed for 3 years (mean 19.8 months) found that the group had symptoms similar to fibromyalgia, depression, and sleep disturbance.<sup>6</sup> In a study of 369 SARS survivors, 40.3% experienced chronic fatigue syndrome 3.5 years after being diagnosed.<sup>7</sup> Viral infections like Epstein–Barr have been linked to chronic fatigue.

Avascular necrosis of the hip was commonly reported as a side effect due to the high-dose steroid treatment.<sup>2</sup> A 15-year follow-up study demonstrated that in the first year, 21% (17) of patients had some form of avascular necrosis on the femoral head of the hip joint. Over time, the clinical stage of femoral head necrosis actually progressed in some of these patients from 2003 to 2007. After 2007, the clinical stage of the femoral head necrosis stabilized in all patients.<sup>5</sup>

The last two common complications that were associated with post-hospitalization due to SARS were a reduced health-related quality of life (HRQoL) and poor mental health. At the 1-year follow-up time, the HRQoL was continually lower in the SARS survivor group compared to that of the normal control group assessed by utilizing a standardized 6-minute walk and a 36-item Short-Form General Health Survey.<sup>3</sup> In regard to SARS-associated poor mental health, a study reporting on a 5-week follow-up of 101 patients found that 25% experienced anxiety and 14% reported symptoms of depression.<sup>2</sup> In the same study, 5% of patients reported experiencing severe anxiety or depression 2 months after discharge. Finally, in a 15-year follow-up period, 42.5% (77) of patients experienced at least one active psychiatric illness.<sup>5</sup> While many of these individuals with poor mental health do eventually recover, it is alarming that so many experienced poor mental health is a result of SARS infection.

### 17.3 MERS—Post-Recovery and Long-Term Complications

Ten years after the SARS epidemic in Asia, another deadly coronavirus appeared in the Middle East.<sup>8</sup> MERS emerged in Saudi Arabia and was largely contained to the Arabian Peninsula, but in 2015, there was an outbreak in South Korea.<sup>9</sup> Mortality analysis of MERS-CoV revealed a 29.8% overall mortality rate, but a 45.2% mortality rate for those above the age of 60.<sup>10</sup> Similar to SARS, respiratory illness was the largest complication in MERS.

In a study that looked at 73 patients who had MERS, 25% (18) of patients did not have pneumonia, while the remaining 75% of patients experienced varying severities of pneumonia.<sup>11</sup> After adjusting for multiple variables, the study found that DLCO and FVC were significantly reduced among patients who presented with pneumonia 1 year after, and that it was a dose-dependent relationship—those with more severe pneumonia having lower DLCO and FVC values.<sup>11,12</sup> A substantial number of patients recovering from MERS develop lung fibrosis on imaging studies.<sup>9</sup> As in the case of SARS, reduced lung function and pulmonary fibrosis were the primary results in patients who recovered from MERS.

Aside from respiratory complications, the MERS-CoV infection also resulted in neurological complications and chronic fatigue syndrome. In a case report published by Algahani, Subahi, and Shirah, the authors present two cases of individuals developing a neurological complication as a result of acquiring MERS. In one case, the patient developed an intracerebral hemorrhage due to platelet dysfunction,

disseminated intravascular coagulation, and thrombocytopenia.<sup>12</sup> In the second case, the patient developed critical illness polyneuropathy. In regard to the development of chronic fatigue syndrome, around 54% of patients who have survived the MERS-CoV infection ended up developing the syndrome within a 2-year time span after being discharged from the hospital.<sup>12</sup>

The final major complication should be discussed in the reduction of quality of life in survivors of the MERS-CoV virus. Among those with different disease severities, patients with greater disease severity had a significant ( $p < 0.05$ ) reduction in the quality of life compared to those who experienced a lesser disease severity.<sup>13</sup>

Overall, the SARS-CoV and MERS-CoV caused a plethora of different complications that provide a framework to better understand what pathologies to expect from SARS-CoV-2. Respiratory, neurological, chronic fatigue syndrome, reduced quality of life, bone-related issues, muscle weakness, and poor mental health are complications that needed to be considered for COVID-19.

## 17.4 Post-Recovery Phase of COVID-19

The first wave of COVID-19 pandemic is sweeping across the world, and much of the initial research was focused solely on understanding its health-related impacts, including respiratory issues, coagulopathy and cardiovascular-associated problems, and pediatric inflammatory syndrome found to be associated with the virus.<sup>14–16</sup> As the pandemic evolves with some countries managing to control and reduce transmission, and others struggling to bring it under control, there is more research discussing post-recovery complications of COVID-19 and eventually, long-term complications associated with it. As more information becomes available, this section will adapt and expand.

The first, and most pressing, question that arises after recovering from COVID-19 is whether an individual develops a robust immune response to the virus that prevents reinfection. The recent literature indicates that detectable levels of IgM and IgG antibodies develop and can be tested for a few days after most individuals are infected with SARS-CoV-2,<sup>17</sup> but it is not definitive whether these are protective. There have been cases in which patients who are discharged return a few days later with positive viral RT-PCR levels, even after having been undetectable during discharge.<sup>18</sup> It has not been established whether this is a new infection, reinfection, or reactivation. There is evidence to demonstrate the presence of neutralizing antibodies and a cellular immune response in macaques, but nothing yet has been established in live humans.<sup>18</sup>

The follow-up question then attempts to determine if these antibodies aid in the clinical outcome of patients. While it has been demonstrated in a small nine person study that more antibodies are produced in a more severe case of COVID-19, the relationship between antibody levels and clinical outcome has not been established. This is further complicated by the idea that patients with less severe presentations of COVID-19 recover before seroconversion occurs.<sup>17</sup>

As part of the coronavirus family, SARS-CoV-2 affects lung function in post-recovery especially in severe cases where patients develop acute respiratory distress syndrome (ARDS). In one study where 22 (16%) patients developed ARDS, the long-term complications were not yet established but experts postulated the potential for the virus to develop pulmonary fibrosis.<sup>19</sup> A radiology study of 21 patients demonstrated that maximum lung involvement occurs at day 10 post-infection, which can be easily seen as ground-glass opacities with crazy-paving patterns on lung CT.<sup>20</sup> Additional scans post day 14 have shown a gradual resolution of consolidation and a decrease in lung involvement, hence indicating full recovery. On the other hand, in another radiology study of 70 patients, 66 (94%) of patients had residual lung disease at hospital discharge with 60% showing ground-glass opacities on lung CT and 74% showing pure ground-glass opacity on lung CT.<sup>21</sup>

While there is not any clear evidence on post-recovery clinical lung outcomes, on a more anecdotal basis, Dr. Owen Tsang Tak-yin, Medical Director of the authority's Infectious Disease Centre at Princess Margaret Hospital in Kwai Chung, has noted that some patients experience a 20–30% decrease in lung function post-recovery.<sup>22</sup> Given this commentary, it is essential that further studies be done both via radiology and via clinically in order to determine the effect of COVID-19 on respiratory outcomes.

The next complication that has been found in COVID-19 patients is the development of cardiac complications. In a case report of 138 patients, 16 (7%) of patients developed arrhythmia, while 7.2% developed some form of acute cardiac injury.<sup>23</sup> Other studies have shown that COVID-19 patients present with higher cardiac troponin I and BNP levels indicating myocardial involvement.<sup>24,25</sup> Additionally, anecdotal evidence has shown a higher incidence of cardiac cases such as acute-onset heart failure, myocardial infarction, and myocarditis in COVID-19 patients.<sup>23</sup> Given the nature of SARS-CoV-2 affecting the heart and cardiovascular system, cardiac injury is highly probable and needs to be accounted for in the future COVID-19 treatment.

There are also neuropsychiatric and central nervous system (CNS) complications that arise in COVID-19 patients. COVID-19 CNS disease has been linked with encephalopathy, encephalitis, acute disseminated encephalomyelitis, meningitis, ischemic and hemorrhagic stroke, venous sinus thrombosis, and endothelialitis.<sup>26</sup> In the peripheral nervous system (PNS), COVID-19 PNS disease has been associated with dysfunction of smell and taste, muscle injury, and the Guillain–Barre syndrome.<sup>26,27</sup> These findings and associations suggest that it is important to consider these complications during the post-recovery phase and longer-term follow-up of COVID-19 survivors.

The final complications that have yet to be studied but need to be addressed in the post-recovery phase of COVID-19 are its effect on mental health and quality of life and the development of chronic fatigue syndrome. Given the similar findings found between SARS and MERS, it is essential to look at these complications in the post-recovery phase of COVID-19. Previous epidemics have set the groundwork on what to investigate in months and years after the initial outbreak of SARS-CoV-2.

While the data is quite limited in regard to COVID-19, the similarities and differences can be easily seen between the previous two epidemics and the current pandemic. This chapter provides an in-depth overview of what was found in the SARS and MERS outbreaks that allows for a potential framework that can be used to study the current COVID-19 outbreak. This chapter has then identified complications that have been studied and need additional investigation in the current COVID-19 outbreak. As time progresses and further data becomes available, it is essential to continually build on the foundation that has been set in this chapter.

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# Personal Protective Equipment (PPE) and Hospital Preparedness for COVID-19

## CHAPTER 18

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### List of Abbreviations

CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
DIB	Doing It's Best
EMS	Emergency medical services
NIOSH	National Institute for Occupational Safety and Health
PPC	Pandemic Preparedness Committee
WHO	World Health Organization

### 18.1 Introduction

The focus of this chapter is to describe a hospital's response to a coronavirus disease 2019 (COVID-19) outbreak in their area—including the ideal personal protective equipment (PPE) and the protocol necessary for preparation.

### 18.2 Personal Protective Equipment

All hospital personnel should have donned PPE prior to entering the room of a patient with COVID-19. This includes, but is not limited to, the use of eye protection, gowns, face masks, respirators, and gloves.<sup>1</sup>

*Eye protection:* Eye protection is necessary to reduce the potential for droplet transmission between the air and the eyes. The World Health Organization (WHO) has found that the use of eye protection is associated with a decreased risk of infection.<sup>2</sup> It is often not considered, but eye protection can be an effective way to reduce the spread of infection in both the community and the hospital setting. In the context of a widespread shortage of PPE, it is prudent to limit the use of medically appropriate goggles to health-care workers. Protection from droplet transmission is only effective if the peripheral areas of the eyes are covered along with the front, so



protection in the form of splash-proof safety goggles or a face shield reaching the front of both ears is recommended. Other forms of eye protection, such as swimming goggles or face shield glasses, can be used in the community without fear of depleting medical resources. In the event of limited supply, hospitals may cancel elective procedures that would require the use of eye protection.

*Gowns:* Since COVID-19 can be spread through fomite transmission, it is necessary for health-care personnel to don gowns while treating infected patients. Proper disposal of gowns will prevent the virus from being spread by the health-care personnel's clothing after contact with a patient. For this reason, ideal gowning should include full-length gowns with shoe covers, leaving no civilian clothing exposed to the environment of the patient's room. This protocol may need to be adjusted depending on availability at individual hospitals. The use of polyester or polyester-cotton gowns, which can be safely washed and reused, can help mitigate issues with limited supply.

*Face masks:* Ideally, covering of the mouth should be accomplished through the use of a respirator. If respirators are not available or are in short supply, a face mask can be used. Face masks provide two-way protection, preventing contact with the health-care personnel wearing the mask and preventing the spread by the potentially exposed person wearing the mask. Face masks have been shown to dramatically reduce the risk of infection. A review by the WHO found that a person wearing a face mask is half as likely to become infected than a person not wearing a face mask.<sup>2</sup> A recent study on the rate of transmission before and after mask mandates (April 8 to May 15) in 15 US states and the District of Columbia found that mask mandates led to a slowdown in daily COVID-19 growth rate.<sup>3</sup> After 5 days, the daily growth rate was 0.9 percentage-points lower compared to the 5 days prior. After 3 weeks, the daily growth rate had slowed down by 2 percentage-points. The authors note that by May 22, as many as 230,000–450,000 cases had been averted.<sup>8</sup>

The reduction in transmission in a health-care setting is even more dramatic with the use of face masks, largely due to proper fitting and consistent use (Figure 18.1). Despite the increased risk of exposure in a hospital, health-care workers are 0.30 times as likely to contract the virus as opposed to only half as likely.<sup>1</sup> Proper use of face masks can counteract the increased risk of infection. In the event of limited supply, it is admissible to use face masks past their shelf life. If a box of face masks has lasted past its shelf life with no visible degradation of the material, it can be used in situations of crisis capacity.

In the context of COVID-19, the main difference between protecting the airway with a surgical mask and protecting the airway through use of a respirator is related to the size of the coarse particles released from a patient's breath. Breath particles are designated either as "droplets" or as "aerosol." Droplets are defined as particles greater than 5  $\mu\text{m}$ , and aerosol consists of particles smaller than 5  $\mu\text{m}$ . Face masks and respirators provide protection from COVID-19 transmission from both droplets and aerosol, but respirators provide a higher degree of protection from aerosol.<sup>4</sup> This is particularly important in contexts such as the intubation of an affected COVID-19 patient, where the person performing the intubation is more likely to come into contact with aerosolized particles that have a high viral load.



**Figure 18.1** The 14 masks used in the test.<sup>7</sup>

In the United States, there are seven types of particulate filtering face-piece respirators that are approved for use by NIOSH (the National Institute for Occupational Safety and Health).<sup>4</sup> They are classified based on two parameters: their resistance to oil and the percentage of airborne particles they can filter. Those that are not resistant to oil are classified N, those that are somewhat resistant to oil are classified R, and those that are strongly resistant to oil are classified P. They can filter, either at least 95% of airborne particles, at least 99%, or at least 99.97%, designating them by the numbers 95, 99, or 100. The seven available types are the N95, the N99, the N100, the R95, the P95, the P99, and the P100. Of these, the most widely available and widely used is the N95.

The N95 respirator is the standard in the United States for personal airway protection, and is also approved by the WHO for the purpose of preventing COVID-19 transmission to health-care workers. The N95 has been shown to be more effective at preventing infection than face masks, including single-layer, 12-layer, or 16-layer

cotton masks.<sup>5</sup> The N95 is comparable to the FFP2 which is certified for use in Europe, the KN95 in China, the P2 in Australia and New Zealand, the Korea 1st class respirator in Korea, and the DS2 in Japan.<sup>6</sup> Due to availability, it is not recommended for the general public to use them in the event of a pandemic. They should be limited to use by health-care professionals who need to treat afflicted patients. Ideally, patients with COVID-19 in hospitals should be placed in rooms with airborne isolation, so only the personnel directly in contact with the patients should require the use of respirators. This is the most effective way to maximize a limited supply.

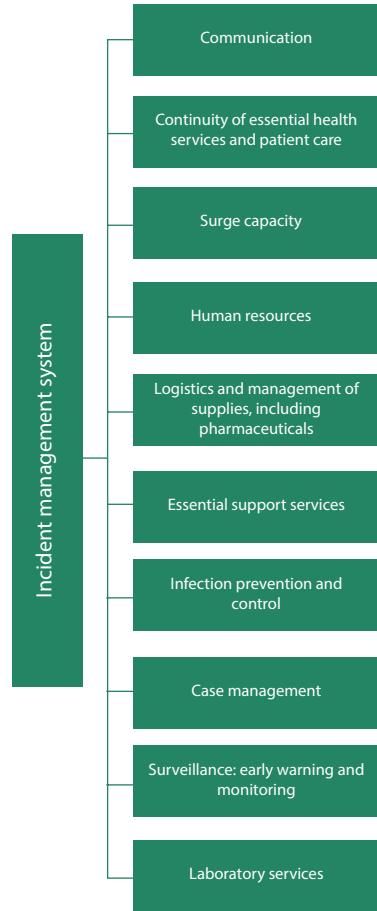
Surgical-grade masks are next most protective, but they can be costly and contribute to landfill waste. The evidence on homemade cotton masks is still emerging, but researchers from Duke University cobbled together a low-cost laser device and conducted a study comparing 14 different types of face coverings.<sup>7</sup> The results showed that fitted N95 masks followed by surgical masks blocked the greatest amount of droplets. N95 masks with valves were less effective. Masks made in three layers or more with vacuum cleaner bags or heavy weight quilter's cotton were effective, but bandanas and neck fleeces were among the least effective. Wearing a neck fleece was actually worse than not wearing anything because the neck fleece actually makes droplets proliferate in the air.

In COVID-19, viral load peaks in the days before onset of symptoms, speaking is enough to dispel virus-carrying droplets, and asymptomatic people can transmit disease. Centers for Disease Control and Prevention (CDC) and WHO guidance recommends that everyone wear masks to slow down the rate of transmission. If 80% of people wear masks, it could reduce transmission more than lockdowns, and according to the Institute of Health Metrics and Evaluation if 95% of Americans wear masks, then 30,000 deaths can be prevented by October.<sup>8</sup>

*Potential Impact of PPE on Patients:* PPE such as face masks, eye protection, and respirators have all been shown to reduce the transmission of COVID-19 and protect health-care workers. The major downside to the use of such strict PPE protocol is the perception of reduced empathy among the patients who are being cared for. Some studies have shown that the use of face masks and face shields can lead to less effective communication between care providers and patients, and feelings of discomfort among patients. Patients experiencing isolation in a hospital are at risk for post-intensive care syndrome, which can be exacerbated by the lack of exposure to live human faces over an extended period of time.<sup>7</sup> Fortunately, there are steps we can take to mitigate these issues, as well.

There are many steps health-care workers can take to humanize themselves and mitigate the psychological effects of prolonged isolation in patients with COVID-19. Some hospitals have added virtual visits between health-care personnel and their patients, allowing them an opportunity to interact without PPE. Another simple solution is the PPE portrait project, where health-care workers keep disposable pictures of themselves attached to their PPE after donning them so that the patients can associate faces with their caretakers. This was started during the Ebola project in Africa, and has been implemented in some hospitals in the United States during the COVID-19 project. Anecdotally, both patients and health-care workers have reported feeling a stronger sense of connection due to the introduction of PPE portraits.

**Figure 18.2** The WHO’s hospital preparedness schematic for COVID-19.



### 18.3 Hospital Preparedness

In the event of an emerging pandemic, how should a hospital respond? What steps need to be taken to ensure preparedness for a potential pandemic? What infrastructure needs to be in place in order to make sure that a hospital can do its part in mitigating the effects of a COVID-19 outbreak? To answer these questions, let’s look at the response by the fictional Doing It’s Best (*DIB*) hospital.

At DIB, the Pandemic Preparedness Committee (PPC) stays in constant contact with the WHO and the CDC as well as global news sources to stay informed of outbreaks everywhere in the world. They establish a specific location in the hospital to be the center of coordination in the event of a pandemic. This location is equipped with the ability to communicate throughout the hospital as well as the local news, government, and even the WHO. The PPC is organized according to the WHO’s hospital preparedness schematic<sup>9</sup>, shown below (Figure 18.2).

The PPC consists of 11 members, one person at the head of the committee and 10 members who are each responsible for one of the key components of the incident response delineated by the above schematic.

1. The PPC Communication coordinator is responsible for gathering accurate information and communicating this information to the hospital staff and local community to ensure communal, coordinated, and evidence-based decision-making.
2. The Continuity coordinator maintains hospital services that must be continued and diverts resources away from hospital services that must be postponed in the event of a pandemic.
3. The Surge capacity coordinator keeps inventory of the hospital's resources and develops contingency plans for an acute increase in the demand for such resources.
4. The HR coordinator ensures adequate staff will be available to respond to a pandemic.
5. The Logistics coordinator communicates with DIB's suppliers, works in conjunction with the Surge capacity coordinator to be aware of inventory, and maintains an influx of necessary supplies in the event of an acute increase in need.
6. The Essential Support Services coordinator focuses on maintaining the continuity of laundry services, waste management, cleaning, and other support services at DIB.
7. The Infection Prevention coordinator is responsible for ensuring compliance with infection prevention protocol.
8. The Case Management coordinator is responsible for triage of patients.
9. The Surveillance coordinator is a trained epidemiologist who maintains contact with the WHO and CDC's surveillance programs.
10. The Laboratory Services coordinator is responsible for ensuring the availability of testing as well as the proper implementation or abstention from the use of tests.

The head of the PPC oversees all ten areas to ensure a coordinated response. Each member trains a prospective replacement who could potentially replace them in the event of an emergency. This ensures continuity of decision-making if any of the members of the PPC are incapacitated during a pandemic.

When the Surveillance coordinator identifies an outbreak that may affect their community, the Communication coordinator immediately launches an awareness program that informs the hospital personnel about the potential outbreak as well as the key symptoms and history that would lead to the identification of infected patients. This is a process that the PPC and the employees would have already been accustomed to, because it was set in motion in the event of SARS, MERS, H1N1, Ebola, and other potential outbreaks that never made it to the news cycle.

The PPC becomes aware of COVID-19 in the early stages of the outbreak through the CDC, which is in close contact with the WHO's Global Influenza Programme

that facilitates the identification and surveillance of flu-like viruses across the world. As a result, the health-care workers at DIB are primed to be on the lookout for any patients with fever, malaise, and dry cough. Any patient presenting with these symptoms can be recognized upon admission and regarded as potentially infected with COVID-19.

Prior to the outbreak, the Case management coordinator would have already assembled a team of trained hospital personnel who were specifically assigned the task of handling triage in the event of a pandemic. As soon as they receive word of an outbreak involving an airborne upper respiratory infection, they work with the Surge Capacity and Logistics coordinators to take inventory of face masks, and make sure there will be enough available so they can be given to any patients being admitted with symptoms suggesting COVID-19. They in turn train the admission staff to recognize the symptoms of fever, malaise, and dry cough to maximize the number of people on the lookout for patients that should be offered face masks.

The waiting areas are reorganized in order to keep patients 6 ft apart as well as direct patients with COVID-19 symptoms to a designated area. Simultaneously, the PPC contacts local news sources and advertisers who help them spread the awareness of COVID-19 in their community and encourage patients to utilize phone and Telemedicine consultations in order to minimize the risk of spreading the virus. The team also develops a written set of instructions about which patients would require admission, testing, and potentially be put on a ventilator, incorporating considerations such as age, comorbidities, and upcoming nonelective surgeries. The team is also in constant contact with the local emergency medical services (EMS) agencies that service DIB in order to identify potential COVID-19 patients being brought via ambulance so that the triage process for them can be done ahead of time. Every staff member in the hospital is informed to report potential cases to the PPC, and the PPC immediately reports any confirmed case to the local health department and the CDC.

DIB is prepared to use the proper PPE and to isolate potentially infected patients. As soon as a potential COVID-19 patient is identified, a systematic communication method relays the information between the front desk admissions and hospital personnel responsible for setting up an isolation room, complete with an air filtration system to minimize the presence of airborne virions. Personnel donned with proper PPE escort the patients to their rooms.

Potentially infected patients are tested depending on the type of care the patients may need. If the patients are young, otherwise healthy, presenting with mild symptoms, not scheduled for an upcoming nonelective surgery, or free of any comorbidities, they are not tested. Whether they are positive or negative for the virus, these patients are sent home and advised to self-quarantine. If patients are older, functionally limited, presenting with severe symptoms, scheduled for an upcoming nonelective surgery, or positive for comorbidities, they are tested. A positive test means that their hospital stay will continue with isolation protocol.

The staff at DIB are diligent about preventing spread of the virus within the hospital from infected patients. Every hospital employee who needs to enter an isolation room does so with proper attire, complete with gloves, eye protection, respirator,

gown, and shoe covers. After time spent inside of an isolation room, no employee makes contact with the nonisolated section of the hospital without a changing and washing protocol. Outside the isolation setting, the employees wash their hands regularly, practice physical distancing, wear surgical masks at all times, and are regularly screened for COVID-19 symptoms. Let's examine each part of their infection prevention plan *other than* isolation.

*Hygiene:* Alcohol-based foam hand sanitizer dispensers are installed in convenient locations throughout the hospital, and the staff are accustomed to a “foam-in, foam-out” rule where hands are sanitized before and after every patient encounter. Sanitizer is used at least every two hours even without patient encounters.

*Physical Distancing:* Staff at DIB maintain 6 ft of distance between each other and with patients unless closer contact is necessary for proper medical care. Elevator capacities are adjusted to allow passengers to maintain the distance. Physical Plexiglas barriers are incorporated at nurse's stations and reception desks.

*Masks:* The PPC takes inventory of masks and finds that their supply cannot support a worsening pandemic. So, they mandate masks be worn by all health-care workers and all symptomatic patients. Once their mask supply is replenished and ready to handle the pandemic, *all* individuals in the hospital are required to wear masks, including non-health-care staff and all patients regardless of symptoms or diagnosis.

*Screening:* No staff member is allowed in a DIB hospital building if they are positive for any symptoms of COVID-19 in the past three days, including fever, dry cough, sore throat, or a loss of taste sensation. If a staff member has had such symptoms, they must have two negative COVID-19 tests before being considered for return to work.

Over time, these infection prevention protocols become a normal part of DIB's culture and are not seen as an inconvenience or imposition on the people who are in the hospital. DIB hospital manages to help patients, prevent spread of the virus, and minimize the death toll of the pandemic until time and new information brought the virus under control.

What were some key steps that DIB took in order to accomplish this? Some key points are below:

1. Appoint a committee for the express purpose of pandemic preparedness.
2. Maintain a constant communication with the WHO, CDC, and local health departments.
3. Write down a specific plan that describes triage policy changes in the event of a pandemic, as well as plans on how to train personnel about recognizing potentially infected patients.
4. Train and rehearse the plan.
5. Implement the plan before a pandemic arrives in the local area.
6. Communicate with local news sources, and spread information about the pandemic to the local community.
7. Maintain a strict protocol to prevent nosocomial infections, involving a comprehensive plan incorporating strict hygiene protocol, physical distancing, mandatory wearing of face masks, and regular screening for COVID-19 symptoms.

Dr. Atul Gawande recommends four pillars to effectively stem the spread of COVID-19—hygiene, distancing, screening, and masks.<sup>10</sup> The fifth pillar, in Dr. Gawande’s strategy, is culture, in hospitals and general community settings, that requires people to care about their own safety as well as the safety of others.<sup>11</sup> It means following rules and noting when such rules are lapsing, and being comfortable in pointing out when standards are slipping.

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## List of Abbreviations

BAL	Bronchoalveolar lavage
CDC	Center for Disease Control
COVID-19	Coronavirus disease 2019
DNA	Deoxyribonucleic acid
FIA	Fluorescent immunoassay
FIND	Foundation for Innovative New Diagnostics
GISAID	Global Initiative on Sharing all Influenza Data
IgG	Immunoglobulin G
NAAT	Nucleic acid amplification test
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

## 19.1 Introduction

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as an unprecedented public health threat. As an airborne virus, it is largely transmitted via respiratory droplets with the first symptoms appearing around 5 days after infection (ranging from 2 to 14 days).<sup>1</sup> However, unlike other coronaviruses, a sizable portion of person-to-person transmission of SARS-CoV-2 occurs before infected individuals develop symptoms (presymptomatic) or never develop any symptoms (asymptomatic).<sup>2</sup>

A country's ability to contain COVID-19 outbreaks depends on identifying and isolating positive cases, and quarantining their contacts. Large-scale diagnostic testing is essential since it allows countries to track viral spread within communities, to safely reopen economies and return life to the new normal, and to better manage clinical progression of illness. Early detection of COVID-19 can aid in the

management of patients and prevent deaths. This chapter focuses on diagnostic testing currently available for COVID-19, and assesses their effectiveness in accurately detecting positive cases.

## 19.2 Background

The genomic sequence of the SARS-CoV-2 was released on January 10, 2020,<sup>3</sup> and it was soon followed by four other genomes deposited two days later in the viral sequence database curated by the Global Initiative on Sharing all Influenza Data (GISAID).<sup>4</sup> As a result of this early sharing of the genome, companies and research groups across the world quickly worked toward developing diagnostic test kits. Researchers from Germany at the German Center for Infection Research (DZIF)<sup>5</sup> at Charité in Berlin developed the first laboratory assay to detect the virus that served as the basis for the first diagnostic kits shipped by the World Health Organization (WHO) to its regional offices on February 2 along with guidance on their use.<sup>6</sup> Aggressive testing in Hong Kong, Republic of South Korea, Singapore, and Taiwan helped to contain transmission (discussed in Chapter 23). Even European countries relied on scaling up testing to contain outbreaks, isolate infected individuals, and quarantine their contacts. The WHO recommended that governments test as many people as possible and that the rate of positivity in testing should remain at 5% or lower for at least 14 days before reopening and lifting stay at home orders and lockdowns.<sup>7</sup>

## 19.3 Types of Tests—NAAT, Antibody, and Antigen

Two types of diagnostic tests were being used to detect COVID-19. First, the real-time reverse transcriptase polymerase chain reaction (RT-PCR), a nucleic acid amplification test (NAAT), and second, serological tests that rely on host immunoglobulin G (IgG) or IgM, interleukins, and other host components. The RT-PCR, considered the gold standard, was usually done by swabbing the nose or mouth for the virus. From the swab sample, a specific section of the viral genome reverse-transcribes the viral ribonucleic acid (RNA) into deoxyribonucleic acid (DNA) and amplifies it through PCR to detectable amounts of the virus. The test requires a laboratory and can also be carried out on automated platforms known as point-of-care diagnostic testing like the Abbott ID NOW. The results can take several hours to complete, and RT-PCR testing requires test kits and materials from nose swabs to chemical reagents, as well as trained health-care professionals to administer.<sup>8</sup>

RT-PCR testing is nearly 100% accurate, but its accuracy depends on the amount of viral RNA present in the sample, which can depend on a variety of factors such as the timing of the test and the start of infection and/or onset of symptoms, the swabbing technique, and the location of the samples. The viral load samples based on location from within patients can vary. In COVID-19-positive patients, test results, determined by RT-PCR, report the following levels from samples: 93% from

the bronchoalveolar lavage (BAL), 72% from sputum, 63% from nasal swab, 32% from pharyngeal swab, 29% from feces, 1% in blood, and 0% in urine.<sup>9</sup> Scaling up RT-PCR can be expensive. However, recently, a saliva test, SalivaDirect, instead of respiratory swabs is under consideration by the FDA for approval. The test is inexpensive (\$1.29–\$4.37) and doesn't require as many material inputs.

The other test for COVID-19 also under use are the serological tests that detect viral-specific antibodies, IgM or IgG. The presence of antibodies (seroconversion) takes time, depending on severity of the illness and the individual's immune system.<sup>10</sup> Antibodies are typically uniformly distributed in the blood, and therefore, there is less variation. Virus-specific antibody, IgM, rises 3 days after the onset of symptoms and begins to disappear as the patient recovers. IgG, which typically rises 10 to 11 days after the onset of symptoms, remains in circulation long after the infection. Serological tests are useful in determining if an individual ever had COVID-19, and should not be used to diagnose current infection because of the slow pace of the antibody response or cross-reactivity with other infections, including those caused by other human coronaviruses. Tests administered too soon when the immune response is evolving can result in inaccuracies (discussed next).

At the population level, antibody tests offer a few advantages over RT-PCR testing. Serological tests are easier to administer requiring a small amount of blood, and tend to be less sensitive to spoilage during collection, transport, storage and analysis. Antibody testing is also important for understanding the overall prevalence of COVID-19 in a community or for purposes of population-level studies.

Together, these two types of tests can be helpful in determining clinical significance of a patient exposed to COVID-19 infection (Table 19.1).<sup>11</sup> A note of caution, in the absence of longitudinal data, it is not clear if the presence of antibodies confers long-term immunity (see Chapter 2) and it would be well advised to maintain protective measures.

**Table 19.1** Diagnostic Testing and Clinical Outcome at the Individual Level

Test Results			Clinical Outcome
RT-PCR	IgM	IgG	
+	–	–	Patient is in incubation period of infection
+	+	–	Patient is in early stages of infection
+	+	+	Patient is in active disease
+	–	+	Patient is in late stage of infection
–	+	–	Patient could be in early stage of infection; RT-PCR result may be false negative
–	–	+	Patient may have had COVID-19 and has recovered
–	+	+	Patient may be in the recovery stage; RT-PCR result may be false negative

The currently available, as well as emerging, diagnostic tests are conveniently summarized at the Mass General website: <https://csb.mgh.harvard.edu/covid>.

Antigen tests for COVID-19 can reveal if a person is currently infected with SARS-CoV-2. Almost as accurate as RT-PCR (but with much less sensitivity), antigen tests detect proteins or glycans, like the spike proteins on the surface. These tests take longer to develop than molecular and antibody tests because suitable antibodies for use in the assays must first be identified and produced. But antigen tests are rapid and relatively cheap, and more amenable to point-of-care technology. The FDA has approved one antigen test from Quidel, Sofia SARS Antigen Fluorescent Immunoassay (FIA) [<https://www.quidel.com/immunoassays/rapid-sars-tests/sofia-sars-antigen-fia>], which takes 15 min.

COVID-19 has triggered innovation in diagnostic thinking. For example, the use of genome-editing technology CRISPR developed for cancer treatment is being used for detecting COVID-19. CRISPR-based tests rely on nucleic acid extraction and amplification and can detect as few as 100 coronavirus particles in a swab or saliva sample, and they don't require many specialty reagents or materials.<sup>12</sup> The tests are administered through cartridge-like devices and provide results within an hour, which makes them attractive to use in a variety of settings. Although CRISPR tests are based on RT-PCR, they tend to produce slightly more false negatives in comparison. Nonetheless, CRISPR-based diagnostics could be an important step toward safely reopening society. The FDA, on May 7, approved the first CRISPR-based diagnostic product, Sherlock Biosciences' 1-h test for SARS-CoV-2.<sup>13</sup> Mammoth Biosciences and GlaxoSmithKline are working on a 20-min CRISPR-based test.

There are other radical ideas using nanobiotechnology, biophotonics, and nanofluidics.<sup>14</sup> For example, researchers are working on facemasks embedded with biosensors that could detect the presence of virus or other devices that could display the virus on piece of silicone or paper. It is likely that the next wave of diagnostics could emerge from the intersection of physical and engineering sciences and biology. The US Congress has doubled the annual budget of the US National Institute of Biomedical Imaging and Bioengineering (NIBIB) by an additional \$500 million, and at the same time, the Defense Advanced Research Projects Agency (DARPA) is funding two CRISPR projects that could deliver low-cost, high-volume point-of-care tests.

The US Center for Disease Control (CDC) has developed a new laboratory test that can detect SARS-CoV-2 and influenza A and B viruses at the same time.<sup>15</sup> The CDC Influenza SARS-CoV-2 (*Flu SC2*) *Multiplex Assay* allows laboratories to continue influenza surveillance while testing for COVID-19, and conserves important testing materials that are in short supply. The Flu SC2 Multiplex Assay was issued an Emergency Use Authorization on July 2, 2020.

## 19.4 Sensitivity, Specificity, and Accuracy in Testing

In COVID-19 diagnostic testing, accuracy matters and interpreting test results can be challenging.<sup>16</sup> Validity of a test is measured in terms of its *sensitivity* and *specificity* (Table 19.2). Sensitivity is the test's ability to identify those with infection and

**Table 19.2** Determining Sensitivity, Specificity, and Accuracy

	Disease Yes	Disease No
Test positive	True positive (TP)	False positive (FP)
Test negative	False negative (FN)	True negative (TN)

Sensitivity =  $TP / (TP + FN)$

Specificity =  $TN / (FP + TN)$

Accuracy =  $(TP + TN) / (TP + FP + TN + FN)$

antibodies, true positives—positive test in a patient with disease. Sensitivity levels of tests are very important because patients who are infected but diagnosed as not having COVID-19 can continue to infect others and spread the disease. Specificity is the test’s ability to identify those without infection, true negatives—negative test in a healthy individual. In the case of individuals who are not infected, but determined to be disease-positive, there are not as many concerns in terms of transmission but people could erroneously assume immunity when that is not the case.

Accuracy is the proportion of correct predictions (true positives and true negatives) among the total number of cases examined. Accuracy is based upon the inherent value of the test, and a higher accuracy of a test reflects a combination of higher sensitivity and specificity (note: the term accuracy in layman’s term differs and is more vague from the term as defined here as used in statistics).

The NAATs typically have high sensitivity and specificity under ideal conditions, but in clinical reality, these measures can vary and depend on the quality of specimen collection, the viral load, and duration of illness. RT-PCR is a good confirmatory test, but according to researchers, false-negative results (people who are positive for COVID-19 but test negative) are more common than initially thought. In one study from Johns Hopkins, 1 in 5 persons was found to have a false-negative result.<sup>17</sup> A systematic review reported false-negative rates between 2% and 29% (equating sensitivity to 71–98%).<sup>18</sup>

Antibody tests are increasingly available but tend to be less accurate. The Foundation for Innovative New Diagnostics (FINN), a global nonprofit organization, conducted an independent evaluation of SARS-CoV-2 antibody diagnostic tests (<https://www.finddx.org/covid-19/dx-data/>) and observed that range was between 25% and 75% for sensitivity. In the United States, the FDA had initially loosened its standards allowing companies to sell antibody tests without submitting clinical evidence on the accuracy of the test but it has recently tightened regulations.<sup>19</sup>

## 19.5 Interpretation of Tests: Understanding Predictive Values

Negative and positive predictive values must be considered in interpretations of a COVID-19 test. A negative predictive value is the proportion of true-negative results with total negative results. A positive predictive value, also known as precision, is the proportion of true-positive results with the total number of positive results.

**Table 19.3** Predictive Powers of a Test with 90% Sensitivity and Specificity (5% Prevalence)<sup>20</sup>

Test Result	People with Disease	People without Disease	Total
Positive	4500	9500	14,000
Negative	500	85,500	86,000
Total	5000	95,000	100,000

Predictive value of a positive test:  $4500/14,000 = 32.1\%$ .

Predictive value of a negative test:  $85,500/86,000 = 99.4\%$ .

Accuracy of test:  $(4500 + 85,500)/100,000 = 90.0\%$ .

**Table 19.4** Predictive Powers of a Test with 90% Sensitivity and Specificity (25% Prevalence)

Test Result	People with Disease	People without Disease	Total
Positive	22,500	7500	30,000
Negative	2500	67,500	70,000
Total	25,000	75,000	100,000

Predictive value of a positive test:  $22,500/30,000 = 75\%$ .

Predictive value of a negative test:  $67,500/70,000 = 96.4\%$ .

Accuracy of test:  $(22,500 + 67,500)/100,000 = 90.0\%$ .

It is important to understand that the predictive value of tests changes along with the prevalence of disease,<sup>20</sup> while accuracy remains fixed. Consider a hypothetical situation with a test with 90% sensitivity, specificity, and accuracy. In a community of 100,000 people with 5% prevalence of disease (5000 positive cases) and 90% sensitivity and specificity, there would still be 500 false negatives and 9500 false positives (Table 19.3), and the predictive value of a positive test would only be 32%, meaning 68% would receive incorrect information. In contrast, in a similar community of 100,000 people with 25% prevalence of disease (25,000 positive cases) and 90% sensitivity and specificity, there would be 2,500 false negatives and 7500 false positives (Table 19.4) with a predictive value of a positive test of 75%, meaning 25% would receive incorrect information.

Sensitivity, specificity, and accuracy vary among antibody tests, and their interpretation based upon predictive values must also take into account the prevalence of COVID-19 in a community or country.

For a more visual depiction of this concept, please see

<https://www.youtube.com/watch?v=qtISu7OhkYE&feature=youtu.be>

## 19.6 Conclusion

In conclusion, testing for COVID-19 is critical for containing the disease and safely opening countries. Countries need to put in place testing strategies and use tests that are validated for realistic conditions. It is important to start testing asymptomatic

people who can unknowingly spread COVID-19. Given the uncertainty regarding immunity, all those testing positive for COVID-19 should still maintain protective measures such as wearing masks, practicing hand hygiene, and refraining from large gatherings.

Diagnostic tests should be affordable and easy to use, especially those for screening and for determining prevalence. Serological surveys should be performed regularly in high-risk communities and situations. Diagnostic interpretation of tests must take into consideration not only the inherent accuracy of the tests but also the prevalence of COVID-19 in the community or country. As new diagnostic methods come forward, all people should have equal access to these emerging technological tools.

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# Drugs for Treating COVID-19

## CHAPTER 20

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### List of Abbreviations

BTK	Bruton's tyrosine kinase
COVID-19	Coronavirus disease 2019
CQ	Chloroquine
DNA	Deoxyribonucleic acid
EUA	Emergency use authorization
FDA	Food and Drug Administration
FPV	Favipiravir
HC	Hydroxychloroquine
HIV	Human immunodeficiency virus
JAK	Janus kinase
PEP	Post-exposure prophylaxis
RDV	Remdesivir
RNA	Ribonucleic acid

### 20.1 Introduction

The treatments for COVID-19 can be split up into different categories. It should be noted that there are no FDA-approved drugs for the treatment of COVID-19. However, all treatments right now are experimental. There have been no clinical data that demonstrates benefits with any of these drugs, but the information on drug treatment is rapidly evolving. Many of these drugs were developed prior to the pandemic and have been repurposed from their intended use to treat COVID-19 patients while some are new compounds (Table 20.1).

**Table 20.1** Summary of New and Repurposed Existing Compounds for COVID-19 Treatment

Classification	Drug	Treatment Strategy	Clinical Trials
Antiviral	Remdesivir	Induce premature termination in RNA replication using an adenosine analogue	NCT04401579 (NIH-sponsored)
	Lopinavir/Ritonavir	May target proteases that cleave polypeptides essential for SARS-CoV2 replication	
	Favipiravir	Targets RNA-dependent RNA polymerase preventing SARS-CoV2 replication	NCT04373733
	Oseltamivir	Neuraminidase enzyme inhibitor, which may prevent virion progeny to be released	
Antimalarial	Hydroxychloroquine/ chloroquine	Reduce inflammatory response Possibly prevent viral entry May interfere with viral assembly	NCT04358068 (NIH-sponsored)
Antibiotics	Azithromycin	Mitigate inflammation Could reduce viral replication in RNA viruses	NCT04358068 (NIH-sponsored) NCT04332107 (Phase 3, 2271 participants)
	Clofazimine		
Monoclonal antibodies	Tocilizumab/sarilumab	Antibodies that block IL-6 receptor to diminish cytokine storm effects	NCT04320615 (Tocilizumab, U.S BARDA-funded)
	Canakinumab	Antibody against pro-inflammatory cytokine IL-1 $\beta$	NCT04362813 (phase 3, 450 participants)
Kinase inhibitors	Acalabrutinib	Suppresses immune response reducing cytokine storm effects	NCT04380688 (phase 2, 60 participants) NCT0434619 (phase 2, 140 participants) Both trials are being sponsored by AstraZeneca
	Baricitinib	Inhibits JAK1/JAK2 to reduce inflammatory response May also reduce viral entry	NCT04421027 (phase 3, 400 participants) NCT04401579 (NIH-sponsored, baricitinib with Remdesivir)
	Tofacitinib	Inhibits JAK1/JAK3 lessening inflammatory response	NCT04412252 (phase 2, 240 participants, Pfizer led) NCT04415151 (phase 2, 60 participants, Yale University led)
	Ruxolitinib	JAK1/JAK2 inhibitor to mitigate inflammation	NCT04362137 (phase 3, 402 participants, led by Novartis) NCT04377620 (phase 3, 500 participants)
	Apilimod	Prevents SARS-CoV-2 entry and replication	NCT04446377 (phase 2, 142 participants)

**Table 20.1** (continued)

Classification	Drug	Treatment Strategy	Clinical Trials
Immunomodulator	Anakinra	Antagonist for IL-1 receptor reducing inflammatory response	
Nonspecific anti-inflammatory	Dexamethasone	Glucocorticoid agonist which aids in immune suppression	NCT04381936 (2104 received dexamethasone vs. 4321 received usual care)
	Methylprednisolone	Prednisolone-based glucocorticoid that reduces inflammatory response	NCT03852537 (phase 2 study, Mayo clinic led) NCT04374071 (completed with 250 participants)
	Ciclesonide	Glucocorticoid that is commonly inhaled to suppress immune response	NCT04377711 (phase 3, 400 non-hospitalized patients) NCT04435795 (phase 3, 454 outpatient participants)
	Budesonide and formoterol	Budesonide is an inhaled glucocorticoid steroid to suppress immune response Formoterol is a bronchodilator	NCT04193878 (phase 3, 600 participants, NIH-funded)
Anti-inflammatory	Colchicine	Reduces the secretion of pro-inflammatory cytokines	NCT04322682 (phase 3, 6000 participants)
Antiparasitic	Nitazoxanide	Prevents viral replication in RNA viruses	NCT04359680 (phase 3, 800 health-care workers receiving prophylaxis treatment) NCT04343248 (phase 3, 800 elderly residents receiving prophylaxis treatment)
	Ivermectin	Prevents SARS-CoV2 replication	
Radiation	Radiation	Induces anti-inflammation	NCT04433949

## 20.2 Convalescent Plasma

Convalescent plasma is another experimental therapy that has been postulated. This is when blood is donated from patients who have previously recovered from the virus and the antibodies are then administered to a person who hasn't recovered. This is potentially a pre- or post-exposure prophylaxis treatment, rather than the treatment of acute illness. This procedure has been researched for many years with different viruses, but there is very limited data showing its efficacy for COVID-19. Please see the following chart from MGH summarizing the significant trials and results:

Author	Virus	Methodology	N	Primary Result
Soo 2004(7)	SARS-CoV	Nonrandomized, retrospective, convalescent plasma vs. methylprednisolone	Txt = 19 Comparison = 21	↓ mortality, ↓ hospital stay in convalescent plasma group
Hung 2011 (8)	H1N1 influenza	Prospective cohort, convalescent plasma vs. standard of care	Txt 20 Control = 73	Convalescent plasma associated with ↓mortality and ↓viral load
Hung 2013 (9)	H1N1 influenza	RCT of hyperimmune IVIG (concentrated and fractionated convalescent plasma) vs. normal IVIG	Txt = 17 Control = 18	H-IVIG was associated with ↓mortality and ↓ viral load
Beigel 2019(10)	Influenza A	RCT, high-titer anti-influenza plasma vs. low-titer plasma	Txt = 92 Control = 48	High-titer anti-influenza plasma showed no benefit over low-titer plasma; 34% had adverse events
Van Griensven 2016 (11)	Ebola	Nonrandomized, convalescent plasma vs. standard of care	Txt 99 Control = 418	No significant difference in survival between groups

Recently, there was one trial that showed out of the five patients that received a transfusion, the viral load decreased and the patients clinically improved. However, there are flaws in this treatment because it takes a lot of resources and is expensive. Therefore, as for any of the treatments, additional research needs to be done to weigh the pros and cons.

## 20.3 Antiviral, Antiretroviral

### 20.3.1 Remdesivir

Remdesivir (RDV) is a broad-spectrum antiviral which inhibits viral RNA polymerases by incorporating an adenosine analogue into nascent RNA chains, causing premature termination.<sup>1</sup> Gordon, Tchesnokov, Woolner, et al. (2020) recently proved that the triphosphate form of RDV effectively inserts into the RNA polymerase of MERS-CoV.<sup>2</sup> This mechanism was shown to occur even more efficiently than natural nucleotide pools, making RDV an attractive candidate for further research for targeting SARS-CoV-2. An *in vitro* study by Wang et al. (2020) corroborates this mechanism against SARS-CoV-2 in Vero E6 cells, at a stage post-virus entry.<sup>3</sup> Researchers suggested RDV to be effective in nonhuman primates at its working concentration.

Much investigation is underway to determine the efficacy of RDV for treating COVID-19.<sup>4</sup> Published studies show promising results showing shorter recovery times and clinical improvement, yet one study found no significant clinical benefits.<sup>5</sup>

- In a randomized, double-blind, placebo-controlled multicenter trial, it was found that the drug was not associated with statistically significant clinical benefits. However, there was a reduction in time to clinical improvement that warrants further confirmation. This was the first study of its kind assessing the effect of intravenous RDV for COVID-19, published in late April.<sup>6</sup>
- Another study was published in late May, which was also double-blind, randomized, and placebo-controlled. Researchers conducted trials of intravenous RDV in adults hospitalized with COVID-19. It was found that RDV led to shorter times to recovery than placebo.<sup>7</sup>
- A study published in the NEJM investigated the compassionate use of RDV on patients hospitalized with COVID-19.<sup>8</sup> Patients were intravenously given a 10-day course of RDV. Clinical improvement was defined as live discharge from the hospital, a decrease of at least 2 points from baseline on a modified ordinal scale (as recommended by the WHO R&D Blueprint Group)<sup>8</sup>, or both. It was concluded that RDV led to a clinical improvement of 36 of 53 patients (68%).

RDV is one of the few drugs to show benefit in COVID-19. *Importantly, RDV is an investigational drug and is not FDA approved for any indication at the present time.* It was only given to hospitalized patients on a compassionate use basis in late January and in clinical trials since February. Initially, the US Department of Health and Human Services was the sole allocator of the drug during a five-month period. As of October 1, 2020, its distribution responsibilities have been returned to the hands of Gilead Sciences, Inc.

On May 1, 2020, the FDA issued Veklury (remdesivir) for treatment of hospitalized patients with severe COVID-19. Patients with severe disease were defined as patients with oxygen saturation (SpO<sub>2</sub>) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO). On August 28, 2020, the FDA reissued the May 1st letter and expanded the authorized use of the drug. Now, its use is no longer limited to patients with severe coronavirus disease.

### 20.3.2 Lopinavir/Ritonavir

Lopinavir and ritonavir are two structurally related protease inhibitors that are coadministered or coformulated. Lopinavir is a selective inhibitor of the human immunodeficiency virus (HIV)-1 protease, arresting its maturation and decreasing further infectivity. Ritonavir has a similar activity, however not as effective due to the initial hepatic metabolism. The purpose of coadministration is for low-dose ritonavir to

inhibit metabolic inactivation of lopinavir, acting mainly as an enhancer in an enzymatic kinetics context.<sup>9</sup> This drug combination is widely used for treating HIV-1 infections, ultimately by suppressing plasma viral load.

Pre-pandemic literature shows evidence of lopinavir/ritonavir leading to better clinical outcomes for treating SARS.<sup>10</sup> As of June 24, 2020, there are 28 active trials that include the usage of lopinavir/ritonavir as a primary or control treatment for COVID-19 (ClinicalTrials.gov, 2020).

There is evidence of some effectiveness with use of lopinavir/ritonavir as part of a combination with other drugs; however, further confirmation is required. A notable study found a triple combination of interferon beta-1b, lopinavir/ritonavir, and ribavirin to alleviate symptoms and shorten hospital stay for COVID-19 patients.<sup>11</sup> In another study, however, Cao et al. (2020) found no benefit to a lopinavir/ritonavir treatment compared to standard care. Researchers conducted a randomized, controlled, open-label trial in 199 hospitalized patients with COVID-19 with points of comparison: time to clinical improvement, mortality, and detectable viral RNA. NIH guidelines also advise against lopinavir/ritonavir and other HIV protease inhibitors for COVID-19 due to pharmacodynamic evidence of insufficient drug levels when taken orally.<sup>12, 13</sup> The NIH also cited the previously mentioned trial by Cao et al. (2020) in their justification.

### 20.3.3 Favipiravir

Favipiravir (FPV) targets viral replication and transcription by acting as a pseudo-purine nucleic acid, thereby selectively inhibiting RNA-dependent RNA polymerase. It is potent against strains of influenza virus, *arena-*, *bunya-*, and *flaviviruses*, as well as members of the *alphavirus*, *paramyxovirus*, and *norovirus* families. It is also useful for viruses that are resistant to neuraminidase inhibitors.<sup>14</sup> There are currently a few clinical trials assessing the efficacy of FPV for treating COVID-19. A study comparing FPV to the control group administered lopinavir/ritonavir found significant clinical differences in median viral clearance time (4 vs. 11 days), as well as in the improvement of chest imaging.<sup>15</sup> Meanwhile, another study found no significant benefits to FPV in comparison with umifenovir.<sup>16</sup>

### 20.3.4 Oseltamivir (Tamiflu)

Oseltamivir, once converted to oseltamivir carboxylate after ingestion, is a neuraminidase enzyme inhibitor.<sup>17</sup> By binding to the active site of neuraminidase enzyme, progeny virions may not be released from the infected cell, greatly reducing the spread of the virus.<sup>18</sup> However, the use of oseltamivir as a potential drug for SARS-CoV-1 was also explored prior to the COVID-19 pandemic with unpromising results.<sup>19</sup> Despite this, there are currently multiple phase III trials involving oseltamivir, some of which are in combination with other drugs such as FPV and hydroxychloroquine (HC).<sup>20</sup>

### 20.3.5 SNG001

SNG001 is an inhaled medication that delivers interferon- $\beta$  to a patient's lungs.<sup>21</sup> Interferon- $\beta$  is released by the body in response to an infection and possesses multiple antiviral properties.<sup>19</sup> A recent trial of 101 participants suggests that administering SNG001 reduced patients' chances of progressing to a more severe state by 79%.<sup>21</sup> The drug is thought to boost inherent antiviral processes in patients, especially those that have reduced interferon- $\beta$  production due to age or other conditions.<sup>22</sup> A larger double-blinded, controlled phase II trial with 400 participants is currently being conducted.<sup>23</sup>

## 20.4 Antimalarial—Hydroxychloroquine/Chloroquine

Chloroquine (CQ) and HC are antimalarial agents. CQ is used mainly for treating malaria and amebiasis, while HC is used mainly to treat rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus.<sup>24</sup> They function as antimalarials by down-regulation of the immune response against autoantigens. This occurs by disrupting the normal formation of peptide–MHC protein complexes which activate T cells, as a consequence of interference with endolysosomal function and thus, the processing of antigens, in macrophages and other antigen-presenting cells.<sup>25</sup>

There has been much hype and controversy surrounding the use of HC to prevent or treat COVID-19. Also something to note are its well-publicized endorsements by the US president and billionaire Elon Musk. An early French study<sup>26</sup> evaluating HC and HC with azithromycin seemed promising, but has since been widely scrutinized for validity<sup>27</sup>, even by the president of the journal that published it.<sup>28</sup> Another early study which was done in China was initially touted as evidence for the efficacy of HC<sup>29</sup>, but was later questioned due to its lack of peer review. These factors may have partly led to an increase in research trials, as well as an uptick in the public actively seeking out these drugs in late April and May this year<sup>30</sup>. As of late June, there are more than 200 clinical trials studying the efficacy of CQ, HC, and HC in combination with azithromycin (ClinicalTrials.gov, 2020).

More evidence is surfacing that CQ and HC are not effective for treating COVID-19.

- The FDA previously cautioned against their use for SARS-CoV-2 due to risk of heart rhythm problems (QT interval prolongation<sup>31</sup>, ventricular tachycardia). Their latest stance, given on June 15th, is that of strong opposition as the FDA has revoked its emergency use authorization (EUA). They cite a large, randomized clinical trial which showed no evidence of reducing likelihood of death or increasing recovery time—as well as more recent data showing that the recommended dose did not kill or inhibit the virus.<sup>32</sup>
- Published in late May, a meta-analysis of 23 studies concludes that the evidence for use of HC or CQ to treat COVID-19 is “weak and conflicting.”<sup>33</sup> The studies included did not evaluate its use as a prophylactic.



- A paper was published in the *Lancet* which suggested that the use of HC for COVID-19 patients “increased hazard” for heart problems and death.<sup>34</sup> Its findings led to alarm in the health and medical research community that caused some clinical trials to stop.<sup>35</sup> The article has since been retracted after researchers were unable to allow an independent peer review due to confidentiality agreements.<sup>34</sup>
- In June, researchers announced conclusions of the large randomized trial Recovery (Randomized Evaluation of COVID-19 thERapY) stating that they found no clinical benefit of the use of HC in treating the disease. 1542 patients were given HC and compared to 3132 patients who received usual care. No significant difference was observed in patient mortality or hospital stay duration.<sup>36</sup>
- In mid-May, an observational study of 1376 patients was conducted in a large hospital in New York City. Clinical outcomes were compared between patients who were given HC and those who were not. Results showed no significant benefits of HC use in decreasing or increasing risk of intubation or death.<sup>37</sup>

Prophylaxis with HC has also been investigated, and no benefits were identified.

- A randomized and controlled study with 2250 participants was done in Barcelona, Spain. Researchers evaluated the use of HC as a tool for post-exposure prophylaxis (PEP).<sup>38</sup> It was found that there was no significant difference between the treatment and control groups in developing COVID-19.<sup>35</sup>
- Another study published in early June by researchers in Minnesota conducted a randomized, double-blind, placebo-controlled trial to determine PEP efficacy of HC. The study enrolled 821 participants who had had high-risk exposure to COVID-19 patients. Researchers found no statistically significant difference in incidence of COVID-19 between the HC and placebo groups, when taken 4 days after exposure.<sup>39</sup>

## 20.5 Antibiotics

### 20.5.1 Azithromycin

Azithromycin’s antibacterial activity comes from its ability to interfere with bacterial protein synthesis by binding to the 50s ribosome subunit.<sup>40</sup> Although it is prescribed for bacterial infections and not viral, it does have anti-inflammatory and antiviral properties, which may be beneficial in treating COVID-19 patients.<sup>41–43</sup> The NIH is currently funding a study that is determining whether azithromycin administered with HC results in a better outcome.<sup>44</sup> This trial is in its second phase of clinical trials.<sup>45</sup> There are also numerous trials looking into other possible

beneficial uses such as proactive care in ambulances, outpatient treatment, and whether azithromycin alone can improve outcomes in COVID-19 patients.<sup>46–48</sup>

### 20.5.2 Clofazimine

Clofazimine is an antibiotic that has been traditionally used to treat tuberculosis and leprosy, which also possess anti-inflammatory properties. An *in vitro* study, clofazimine appears to have reduced the viral load. There is a phase II study further exploring clofazimine's possible role in treating SARS-CoV-2 infections, including a possible combination therapy with interferon  $\beta$ -1b.

## 20.6 Monoclonal Antibodies

### 20.6.1 Tocilizumab (Actemra) and Sarilumab (Kevzara)

Tocilizumab (Actemra) and sarilumab (Kevzara) are both antibodies that target the human receptor for IL-6, which has been known to be produced at inflammatory sites and to play a key role in chronic inflammation.<sup>49, 50</sup> A large release of IL-6 has also been observed in cytokine storms, and it was speculated that an IL-6 blocker could be used to treat them.<sup>50</sup>

Initial reports of tocilizumab seemed as a promising compound in alleviating effects of cytokine storms and improving clinical outcomes among COVID-19 patients.<sup>51, 52</sup> This has led to numerous studies on tocilizumab in the treatment of COVID-19.<sup>53</sup> Tocilizumab's promising results have also led the US Biomedical Advanced Research and Development Authority to invest 25 million dollars in phase III trials.<sup>54</sup> There are also two clinical trials looking into tocilizumab's therapeutic effects in conjunction with RDV and HC.<sup>55, 56</sup> Despite sarilumab's similarity with tocilizumab, initial results reported by Regeneron and Sanofi (the manufacturers and developers of sarilumab) were not as promising and only those deemed "critically" will advance to phase III studies.<sup>57</sup>

### 20.6.2 Canakinumab (Ilaris)

Canakinumab is a monoclonal antibody against human IL-1 $\beta$ , a pro-inflammatory cytokine.<sup>58, 59</sup> This drug has traditionally been used to treat mainly immune and inflammatory disorders, such as cryopyrin-associated periodic syndrome and Muckle-Wells syndrome.<sup>58, 60</sup>

This drug has been used to treat patients suffering from hyperinflammation due to COVID-19; however, without a study with larger samples and controls, its true efficacy is not well known.<sup>61</sup> There are currently phase III trials being conducted by Novartis, the developer of canakinumab, exploring the efficacy of canakinumab in patients with COVID-19-induced pneumonia that is experiencing cytokine release syndrome (CRS).<sup>62, 63</sup>

### 20.6.3 Leronlimab

Leronlimab is a humanized antibody for chemokine receptor CCR5 and was initially developed for HIV treatment.<sup>64</sup> The company, CytoDyn, that developed this drug has been also exploring other applications such as COVID-19 treatment.<sup>65</sup> Researchers are hoping that by binding antibodies to CCR5, cytokine production can be reduced, which can then alleviate the adverse effects of cytokine storms in COVID-19 patients.<sup>65</sup> Initial results reported by the company showed signs of clinical improvement and relative safety.<sup>65</sup> As of July 29, 2020, there is a phase II, double-blind, controlled study with 390 participants being sponsored by CytoDyn.<sup>66</sup>

## 20.7 Kinase Inhibitor

### 20.7.1 Acalabrutinib (Calquence)

Acalabrutinib is an irreversible second-generation Bruton's tyrosine kinase (BTK) inhibitor.<sup>67</sup> BTK is an important player in B cell maturation, dendritic cell regulation, cytokine production, and phagocytosis.<sup>68</sup> Therefore, it has been used to treat malignancies that are B cell in origin.<sup>69</sup> This also makes acalabrutinib an immunosuppressive, so it is being investigated for treating COVID-19.<sup>68</sup> There are currently two clinical trials that are in phase II seeing if the drug can reduce mortality in COVID-19 patients.<sup>70</sup>

### 20.7.2 Baricitinib (Olumiant)

Baricitinib is a selective inhibitor for JAK1/JAK2 that has been commonly used to treat rheumatoid arthritis.<sup>71</sup> These Janus kinase (JAK) proteins initiate an activation cascade that eventually alters cellular transcription, and have been associated with inflammation.<sup>72</sup> This connection is thought to be caused by the activation of JAK proteins via cytokine receptors.<sup>72</sup> This drug may also provide antiviral properties.<sup>73</sup> Baricitinib also binds to AP2-associated protein kinase 1, which may affect endocytosis and reduce viral entry.<sup>73</sup> However, some have stated that to see this effect requires doses that are much higher than therapeutic doses.<sup>74</sup>

There are currently multiple clinical trials for COVID-19 taking place in multiple countries, some of which are looking to see the effects of combining baricitinib with other medications such as with lopinavir/ritonavir and RDV.<sup>75, 76</sup> Although an initial report suggests promising outcomes when using the baricitinib, the same report recognizes that the study had a small sample size and no randomization.<sup>73</sup>

There are a couple of features that make baricitinib different from ruxolitinib despite both being first generation of JAK inhibitors.<sup>77</sup> Baricitinib is not

metabolized by cytochrome P450 and can be excreted by the kidney, while the opposite is true for ruxolitinib.<sup>77</sup>

### 20.7.3 Tofacitinib (Xeljanz)

Tofacitinib is a JAK inhibitor that specifically targets JAK1, JAK3, and to a lesser extent JAK2.<sup>77</sup> Tofacitinib has been used to treat a wide array of inflammatory and autoimmune conditions such as rheumatoid arthritis, inflammatory bowel disease, and other dermatological disorders.<sup>77</sup>

There are currently at least four clinical trials looking into tofacitinib as a form of treatment in patients with COVID-19, one of which is comparing the drug effects to using HC alone.<sup>78, 79</sup>

### 20.7.4 Ruxolitinib (Jakafi)

Ruxolitinib is a kinase inhibitor that targets JAK1/JAK2.<sup>80</sup> This JAK inhibitor has been mainly used to treat myelofibrosis, a form of cancer affecting the bone marrow.<sup>78</sup> Due to its anti-inflammatory properties, there are currently phase III trials and other studies looking into ruxolitinib in treating cytokine storms associated with COVID-19.<sup>81, 82</sup>

### 20.7.5 Apilimod

Apilimod is phosphatidylinositol-3-phosphate 5-kinase (PIKfyve) inhibitor and seems to influence the maturation and function of endosomes. Its possible roles in treating B-cell non-Hodgkin's lymphoma, lysosomal dysfunction-related disorders, and viral infections have been explored prior to SARS-CoV-2. A study published in July 2020 suggests that the drug may also be useful in preventing the entry of SARS-CoV-2 into human cells as well as replication. There is currently a phase II clinical trial involving COVID-19 outpatients with mild symptoms.

## 20.8 Immunomodulator: Anakinra (Kineret)

Anakinra acts as an IL-1 receptor antagonist.<sup>83</sup> It has been mainly prescribed for patients with rheumatoid arthritis and other autoinflammatory conditions.<sup>84</sup> There have been reports where the drug has been reported to reduce systemic inflammation and alleviate pulmonary symptoms in some COVID-19 patients.<sup>85, 86</sup> There are currently multiple clinical trials exploring the drug's efficacy.<sup>84</sup> This drug may help reduce mortality as there are reports of hyperinflammation and cytokine storms, resulting in mortality of COVID-19 patients.<sup>87</sup>

## 20.9 Nonspecific Anti-inflammatory

### 20.9.1 Dexamethasone

Dexamethasone is a steroid that works as an anti-inflammatory and immunosuppressive by acting as a glucocorticoid agonist.<sup>88</sup> Results of a randomized clinical trial involving 2104 patients seem encouraging, as results show that daily administration of the drug (6 mg either orally or by IV) reduced mortality by a third in ventilated patients and by a fifth in patients receiving only oxygen.<sup>89</sup> However, experts have urged caution as the official papers detailing the results have not been published.<sup>90</sup> The World Health Organization and other countries have previously expressed reservations of using steroids in treating COVID-19 patients, since steroids may suppress the immune system to a higher extent than desired, but they have indicated that these results may change WHO clinical guidelines.<sup>91,92</sup> If further data reinforces the benefits of dexamethasone, this steroid, which is considered inexpensive and widely available, may become a key drug in saving many lives.<sup>92</sup>

### 20.9.2 Methylprednisolone

Methylprednisolone is a corticosteroid that is based on prednisolone, a glucocorticoid, but it is reported to have a higher potency than prednisolone and to have a potency that is five times greater than hydrocortisone in its anti-inflammatory properties.<sup>93</sup> The use of methylprednisolone in treating COVID-19 patients with ARDS as well as preventing the worsening of clinical symptoms has been suggested.<sup>94</sup> A study of 173 participants in Italy has led the Lazzaro Spallanzani National Institute for Infectious Diseases to recommend doctors in considering the use of methylprednisolone in patients that begin to have worsening respiratory functions.<sup>95</sup> Another study of 213 participants by Henry Ford Health System also seems to suggest that the use of methylprednisolone can improve outcomes and help prevent worsening of respiratory functions.<sup>94</sup> More studies are being conducted, including one by the Mayo clinic, to further support the use of methylprednisolone.<sup>96</sup>

### 20.9.3 Ciclesonide

Ciclesonide is a glucocorticoid that reduces inflammation by reducing vasodilation, vascular permeability, and the accumulation of leukocytes and macrophages.<sup>97</sup> It has been regularly used as an inhaled corticosteroid, and there were some early reports suggesting ciclesonide as an effective candidate for treating SARS-CoV-2-induced pneumonia.<sup>98-101</sup> However, there are claims that it is not clear whether or not inhaled corticosteroid is an effective treatment in patients with COVID-19.<sup>102</sup> There are currently multiple clinical trials taking place in Asia, Europe, and North America, including a phase III clinical trial with 400 participants in the United States.<sup>103</sup>

#### 20.9.4 Budesonide/Formoterol

Budesonide is a glucocorticoid steroid that can be delivered via oral inhalation.<sup>104</sup> Formoterol, a long-acting beta agonist, works as a bronchodilator and is routinely administered with budesonide in asthma patients.<sup>102, 105</sup> The NIH is funding a phase III clinical trial of this drug combination in patients with acute respiratory failure, including cases involving COVID-19.<sup>106</sup>

### 20.10 Anti-Inflammatory Colchicine

Colchicine is a compound that is extracted from plants belonging to the *Colchis* genus, and has been used to treat a variety of conditions, including inflammatory ones such as pericarditis.<sup>107</sup> The compound's anti-inflammatory properties can come from multiple mechanisms.<sup>107</sup> Some of which include the reduction in the secretion of certain cytokines such as IL-1 $\beta$ , IL-8, and IL-18.<sup>107-109</sup>

A recent study published from Greece consisting of 105 patients suggests that colchicine may be considered as a possible treatment.<sup>110</sup> However, even the authors of this paper noted that this data is “hypothesis-generating,” and more studies are needed.<sup>110</sup> There are currently multiple phase III trials looking into colchicine, including one that is double-blinded, controlled, and with 6000 participants being conducted in parts of the United States, Canada, and Spain.<sup>111</sup>

### 20.11 Antiparasitic

#### 20.11.1 Nitazoxanide

Nitazoxanide is an antiparasitic drug that targets pyruvate ferredoxin/ flavodoxin oxidoreductase electron transfer.<sup>112</sup> Although initially developed as an anti- protozoan drug, the compound has also shown to reduce replication in RNA and deoxy- ribonucleic acid (DNA) viruses, including ones that are resistant to oseltamivir.<sup>113</sup> There are currently phase III clinical trials where researchers are seeking to determine if nitazoxanide can serve as a safe prophylaxis in health-care workers and the elderly.<sup>114, 115</sup>

#### 20.11.2 Ivermectin

Ivermectin targets invertebrate glutamate-gated chloride channels inducing an influx in chloride.<sup>116</sup> Studies in the past have also indicated that the drug may have antiviral properties causing others to express the possibility of ivermectin as a possible candidate for treating COVID-19 patients.<sup>117</sup> This has led to multiple ivermec- tin-based clinical trials, including one by Johns Hopkins University.<sup>118</sup>

## 20.12 Radiation

Low-dose radiation has been used to treat conditions like pneumonia before the advent of antibiotics, and it is thought to work by inducing anti-inflammatory processes.<sup>119, 120</sup> The use of low-dose whole lung radiation seems to have improved the condition of some COVID-19 patients.<sup>119</sup> On June 16th, 2020, a phase III trial was first posted which seeks to determine whether low-dose whole lung radiation can be better than the current best supportive practices.<sup>121</sup>

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## List of Abbreviations

COVID-19	Corona virus disease
MERS	Middle East respiratory syndrome
VLP	viral-like particle

### 21.1 Introduction

This chapter will briefly discuss viral technologies and categories relevant to corona virus disease (COVID-19) vaccine candidates, which will include advantages, disadvantages, and strategies to illicit immunity for each type of vaccine mentioned. The availability, possible risks, and how mutations may affect the efficacy of these vaccines will also be briefly touched upon.

### 21.2 What Are Viral Vaccines?

Viral vaccines are prepared substances that seek to prevent the manifestation of a disease that is viral in origin, and to prevent the further spread of a viral pathogen.<sup>1</sup> There are multiple different types of vaccines based on their composition, and some of these types are adenovirus vector, mRNA, DNA, live attenuated, inactivated, and subunit.<sup>1</sup> Vaccines are considered as the primary method for preventing viral infections.<sup>1</sup> Vaccinations have been used to contain epidemics and are considered a vital tool in reducing mortality in a pandemic.<sup>2</sup>

### 21.3 What Are the Risks Associated with Viral Vaccines?

The risk a viral vaccine may have is dependent on the type of vaccine as well as the patient's condition.<sup>3</sup> In the case of live vaccines, patients who are sufficiently immunocompromised should not receive some vaccines as they may lead to an adverse



reaction or result.<sup>3</sup> The contents of the vaccine can also pose a risk in some individuals as they can lead to an allergic reaction, some of which may lead to asphyxiation.<sup>4</sup> In other rare cases, vaccine recipients have actually become more susceptible to infection or a more severe manifestation of the disease.<sup>5, 6</sup> This phenomenon is called immune enhancement.<sup>6</sup> Although studies suggest immune enhancement may be unlikely for SARS-CoV-2 vaccine candidates, it is a concern that is plausible enough for experts to express the need to monitor for enhancement during trials and to determine the possibility of enhancement.<sup>6, 7</sup>

## 21.4 SARS-CoV-2 Vaccines in Development and WHO Database

As of September 25, 2020, approximately 42 potential COVID-19 vaccines are being tested in various stages of clinical trials.<sup>8</sup> Over a hundred more are in the pre-clinical phase in development.<sup>8</sup> The World Health Organization has a periodically updated table detailing the type of vaccine, its developer, and its current stage of development (Table 21.1).<sup>8</sup> (<https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines>).

### 21.4.1 Viral Vector Vaccines and Adenoviral Vector Vaccines

Viral vector vaccines exploit the existing viral mechanisms to transport genetic material into the vaccine recipient's cells to express an antigen.<sup>9</sup> These viral vector vaccines can be further differentiated into nonreplicating and replicating versions.<sup>9</sup> An advantage of a replicating viral vector vaccine is dosage sparing and a stronger immune response, which may allow for more vaccines to be available.<sup>9</sup> There are currently 40 viral vector vaccines being developed for SARS-CoV-2 based on the following viruses: the pox virus, the paramyxovirus, the alpha virus, the vaccinia virus, the influenza virus, and the adenovirus.<sup>8</sup> The first vaccine to enter phase III of clinical trials is an adenoviral vector vaccine developed by Oxford University's Jenner Institute.<sup>8</sup> Published data also shows that this vaccine can produce antibodies and a cellular response in recipients who received doses in April 2020.<sup>10</sup>

An adenoviral vector vaccine utilizes the adenovirus, which is a double-strand DNA, nonenveloped virus.<sup>11</sup> Due to its genetic make-up, concerns of integration were expressed, but studies show that adenoviral vector vaccines remain largely unintegrated.<sup>11</sup> Adenoviral vector vaccines have also been attenuated, and its vector has been modified to prevent the possibility of replication, further reducing the possibility of adverse effects.<sup>11</sup> The vaccine being developed by the Jenner Institute also addressed the issue of preexisting immunity to the adenovirus by developing the vector in chimpanzees.<sup>8, 12</sup> Previous work on an adenoviral vector vaccine for Middle East respiratory syndrome (MERS) has shown that an adenoviral vector vaccine can produce a "robust immune response" to a coronavirus, and aided researchers in developing an adenovirus viral vector vaccines for COVID-19.<sup>13, 14</sup> However, trials

**Table 21.1** Types of SARS-CoV-2 Vaccines and Promising Vaccine Candidates

Developer	Type	Stage	Financial Supporters
University of Oxford/AstraZeneca	Adenoviral vector	Phase 3	U.S. Dept. of HHS—\$1.2 billion U.K. Gov.—£84 million CEPI-\$750 million
CanSino Biological Inc./Beijing Institute of Biotechnology	Adenoviral vector	Phase 3 Approved for limited use in China NCT04526990 NCT04540419	China's Ministry of Science and Technology
Gamaleya Research Institute	Adenoviral vector	Phase 3 (approved for limited use in Russia) NCT04530396 NCT04564716	Russian government
Janssen Pharmaceutical Companies/Johnson and Johnson	Adenoviral vector	Phase 3 NCT04505722	U.S. BARDA- \$456 million dollars U.S. Government-\$1 billion dollars for 100 million doses if approved
Moderna/NIAID	RNA	Phase 3	U.S. BARDA—\$483 million Bill and Melinda Gates Foundation—\$20 million CEPI
BioNTech/Pfizer	RNA	Phase 3 NCT04368728	
Sinovac	Inactivated	Phase 3 (approved for limited use in China) NCT04456595	Advantech and Vivo Capital-\$15 million Bank of Beijing-\$8.5 million
Novavax	Subunit	Phase 3 NCT04533399	U.S. Dept. of HHS and DoD-\$1.6 billion CEPI- \$384 million
Inovio Pharmaceuticals	DNA	Phase 2 NCT04447781	U.S. DoD-\$71 million CEPI-\$17.2 million

for the Oxford University/AstraZeneca's vaccine were put on pause in the UK due to possible safety concerns, which have been resolved.<sup>15</sup>

Another adenovirus-based vaccine, being developed by CanSino, is currently in phase III of clinical trials. Unfortunately, current results from this vaccine show the rates of neutralizing antibody production were lower than desired, and side effects reported were relatively high<sup>16, 17</sup> As of September 25, 2020, the WHO has reported 45 vaccine candidates using adenovirus technology of which the most advanced and

promising candidates are from the Oxford University/AstraZeneca, and BioNTech/Pfizer.<sup>8</sup>

### 21.4.2 RNA Vaccines

RNA vaccines seek to induce the expression of a desired antigen in the patient by transporting genetic material into recipient's cells.<sup>18</sup> Moderna's RNA vaccine, an initial forerunner, has begun its phase III trials and is expected to enroll 30,000 healthy participants who will receive two intramuscular injections, spaced 28 days apart, containing 100 microgram injections of mRNA-1273 or a saline placebo.<sup>19</sup> The company has stated that the vaccine may not be available till 2021.<sup>20</sup> Pfizer's vaccine, another RNA vaccine, may also have results early enough for approval in the fall.<sup>21</sup> Both of these vaccines are using lipid nanoparticles to transport RNA for translation and production of the antigen.<sup>22, 23</sup> By using lipid nanoparticles, issues of degradation, which have been associated with RNA vaccines, can be reduced while serving as a method of delivery.<sup>22</sup> Research also suggests that RNA vaccines may elicit humoral and cell-mediated immunity in a single dose.<sup>24</sup> As of September 25, 2020, the WHO has reported 24 vaccine candidates using RNA technology.<sup>8</sup>

### 21.4.3 DNA Vaccines

DNA can also be used to express the antigen in patients and, like RNA vaccines, can illicit a humoral and cell-mediated immune response.<sup>25</sup> There are 16 DNA vaccine candidates as of September 25, 2020, four of these candidates are in phase II trials.<sup>8</sup> However, DNA vaccines have been reported of having lower immunogenicity, and different delivery techniques were explored in response to this phenomenon.<sup>26</sup> One of the major delivery techniques developed is electroporation, the technique being used by Inovio pharmaceutical's vaccine candidate.<sup>25</sup> Electroporation works by creating electrically induced pores to facilitate the entry of the DNA vaccine into the cell.<sup>26</sup> Like adenoviral vector vaccines, concerns of integration seem to be insignificant.<sup>27</sup> Another method to address this issue is the addition of adjuvants, substances that increase vaccine's immunogenicity, to some DNA vaccine candidates.<sup>27</sup>

### 21.4.4 Live Attenuated Vaccines

A live attenuated vaccine is a vaccine that takes a weakened form of the virus to illicit future immunity.<sup>28</sup> Since this kind of vaccine emulates a real infection, an antibody and cell-mediated response that is long lasting may occur.<sup>28, 29</sup> This response can usually be achieved in one or two doses.<sup>30</sup> However, since live

attenuated vaccines emulate a real infection and because there is a small chance a live attenuated vaccine may return to a more pathological form, certain individuals may not be suitable for receiving this form of vaccine.<sup>28</sup> Although there are no live attenuated vaccines in the clinical stage, there are three in development as of September 25, 2020.<sup>8</sup>

#### 21.4.5 Inactivated Vaccines

Inactivated vaccines are vaccines that inject viruses inoculated by using heat, chemicals, or radiation.<sup>29</sup> These vaccines cannot cause infections and can be safely administered to those who are immunocompromised.<sup>29</sup> Some inactivated vaccines may also be stored at room temperature, which may provide logistical benefits.<sup>30</sup> Unfortunately, inactivated vaccines do not create a cell-mediated response and may also require booster doses.<sup>28</sup> To get a desired immune response, multiple doses are also usually required.<sup>28</sup> As of September 25, 2020, there are currently 14 inactivated vaccine candidates, 5 of which are in clinical trials, including three that are in phase III being developed by Chinese companies.<sup>8</sup> Adjuvants are also being added to some of these vaccine candidates, which may lead to dose sparing and therefore more available vaccines.<sup>8, 27</sup>

#### 21.4.6 Subunit Vaccines and Viral-Like Particle Vaccines

Another type of vaccine candidate type are subunit vaccines.<sup>8</sup> Some of which are using adjuvants, substances that increase an antigen's immunogenicity which could allow for more available doses.<sup>31</sup> An inactivated vaccine uses the inoculated form of the pathogen, while a subunit vaccine utilizes a specific portion of the pathogen.<sup>32</sup> Since these vaccines also do not mimic an infection like an inactivated vaccine, the immune response is mainly humoral and not cell mediated.<sup>32</sup> This inability to cause an infection also makes these vaccines safer for the immunocompromised or those with certain health conditions, but it is important to note that the vaccine's effectiveness may be reduced in certain immunocompromised individuals.<sup>3, 33</sup> However, these vaccines usually require multiple doses and/or booster doses to produce sufficient long-term immunity.<sup>29</sup> There are currently 70 subunit vaccine candidates defined by the WHO, 13 of which are in clinical trials as of September 25, 2020.<sup>8</sup>

A more specific type of subunit vaccine is a viral-like particle (VLP) vaccine, and there are 16 VLP vaccine candidates as of September 25, 2020, one of which is in phase II clinical trials, while another is in phase I.<sup>8, 34</sup> A VLP vaccine is constructed utilizing recombinant proteins to create particles that closely resemble the virus.<sup>35</sup> The size and high repetitive structure may lead to high immunogenicity without risk to the immunocompromised due to the lack of genetic material in VLP vaccines.<sup>36</sup> The nature of VLP vaccine production may provide advantages in increasing production.<sup>37</sup>

## 21.5 Who will Get the First Vaccines?

Chinese and Russian governments have approved adenovirus-based vaccines for limited use without conclusive phase III studies, which have raised a concern in the scientific community.<sup>38</sup> Despite initial estimates of a vaccine being available by the end of 2020, experts and company statements are now estimating a vaccine sometimes next year.<sup>39, 40</sup>

Multiple companies have already been investing into vaccine production, but fears that supply will be limited exist.<sup>41</sup> Therefore, vulnerable populations may receive the first doses, including children, the elderly, the immunocompromised, patients with certain preexisting conditions, and health-care workers.<sup>42</sup> Yet, this may also be dependent on the vaccine as there are some reports that suggest that certain vaccines may not be suitable for some of these populations.<sup>43</sup>

## 21.6 Will these Vaccines Protect against a Mutated SARS-CoV-2 Virus?

Whether or not the vaccines in development will prevent mutated forms of the virus remains unclear.<sup>44</sup> The SARS-CoV-2 virus is mutating as expected, and some mutations seem to have affected the spike protein (the molecular target of many vaccine candidates).<sup>45</sup> In order to prevent future strains from evading vaccines, there have been recommendations for future drugs and vaccines to target areas of the viral genome that are relatively constrained.<sup>46</sup> The rate of mutation, however, seems to be slower than that of influenza, about half as slow.<sup>47, 48</sup> Another indicator that mutations may not prevent the efficacy of vaccines is that vaccines can be designed to target multiple sites of the virus, reducing the risk of a mutated virus escaping existing immunity.<sup>49, 50</sup>

## 21.7 Will These Vaccines Produce Long-Term Immunity?

There are multiple studies that suggest effective antibody levels may decline within a few months of SARS-CoV-2 infection.<sup>51, 52</sup> This may be an issue in vaccines that produce primarily an antibody response and may only confer short-term immunity. However, this drop in antibody levels does imply the absence of memory B cells, which may allow the rapid production of antibodies if reinfection occurs.<sup>51, 53</sup>

These studies may also further reinforce the importance of T cells and vaccines that illicit a cellular-mediated response.<sup>52</sup> T cells can also remember pathogens for many years, and once reinfection occurs, they can activate the immune system and kill any cells infected with the virus.<sup>54</sup> Fortunately, the detection of T cells that can recognize SARS-CoV-2 in people once infected and those that received certain vaccine candidates suggest that long-term immunity can be achieved.<sup>55</sup>

## 21.8 Antivaxxers and Vaccine Efficacy

Antivaccination sentiments have been increasing and may affect the rates of vaccinations for SARS-CoV-2.<sup>56</sup> Recent polls seem to show that only half of the US population may be willing to receive a vaccine for COVID-19, which is much lower than some estimates for achieving herd immunity, a phenomenon that can protect unvaccinated individuals if enough of the population become immunized.<sup>56–58</sup>

Populations that are most hesitant may be those with historic mistrust of governmental agencies, such as African Americans due to the Tuskegee Study, where members of the African American community were knowingly given syphilis and denied treatment.<sup>56,57</sup> Widespread hesitation can also be accounted for by other factors like the speed of vaccine development and misinformation.<sup>56</sup> Experts have expressed concerns how the existence of a vaccine may not stop the COVID-19 pandemic unless public opinion changes.<sup>59</sup> John Hopkins Center for Health Security has published a report of strategies and guidance to increase the willingness for receiving a coronavirus vaccine. ([https://www.centerforhealthsecurity.org/our-work/pubs\\_archive/pubs-pdfs/2020/200709-The-Publics-Role-in-COVID-19-Vaccination.pdf](https://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2020/200709-The-Publics-Role-in-COVID-19-Vaccination.pdf))

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# Socioeconomic, Racial, and Cultural Considerations

## CHAPTER 22

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### List of Abbreviations

CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease
SDoH	Social determinants of health

### 22.1 Introduction

Coronavirus disease (COVID-19) has been termed the “great equalizer,” capable of sickening anyone, but the reality is that it has increasingly demonstrated that social inequalities in health are profound.<sup>1</sup> In times of pandemics and epidemics, such differences become even more exaggerated. COVID-19 is not an equal-opportunity killer, and its victims are often the poor and economically vulnerable, living in crowded conditions, including prisons, and those without access to health care. These conditions in which people are born, grow, live, work, and age are known as the social determinants of health (SDoH). The SDoH are conditions. They are shaped by the distribution of money, power, and resources, and are mostly responsible for health inequities in the health status of people seen within and between countries.<sup>2</sup> This chapter examines the SDoH of COVID-19 in the United States and touches upon some critical issues in developing societies.

### 22.2 Social Determinants of Health Framework

The SDoH framework includes five key areas of determinants—economic stability, education, social and community context, health and health care, and neighborhood and built environment<sup>3</sup> that affect peoples’ well-being, functioning, and quality-of-life outcomes and risks (Figure 22.1). Each of these five determinant areas includes a number of subtopics that inform the overall framework (Table 22.1). For example,

**Figure 22.1** The social determinants of health.



**Table 22.1** SDoH Elaborated

Economic Stability	Neighborhood and Physical Environment	Education	Food	Community and Social Context	Health-Care System
Employment Income Expenses/ Debt Support	Housing Transportation Safety Parks Playgrounds Walkability Zip code/ geography	Literacy Language Early education Vocational training Higher education	Hunger Access to healthy options	Social integration Social systems Community engagement Discrimination Stress	Health coverage Provider availability/ accessibility Linguistic competence Quality of care
Health Outcomes: Mortality, Morbidity, Health Status					

under economic stability, subtopics such as employment, food insecurity, housing instability and poverty would be included, and social and community context would include civic participation, discrimination, incarceration, and social cohesion. In addition, SDoH also include access to green spaces; exposure to environmental toxins; and discrimination based on gender, race or ethnicity, immigration status, and religion among others.

Unequal distributions and access to resources, exposure to discrimination, and administrative failures to ensure safety and maintenance all lead to the creation of

phenomena called **health disparities**, that is, difference in outcomes as a result of economic, social, or environmental disadvantages.<sup>4</sup> These are not singular, or individual, acts of injustice, but rather systemic and structural failures in the system and deliberate flaws in the infrastructure of society. In contrast, health equity aims to create situations that would avoid bad health outcomes for people through access to opportunities and resources and instituting certain protections that would reduce the burden of disease on disadvantaged groups.

The COVID-19 crisis has revealed that not all care is delivered equally, and there are gaps in health care and health disparities, which have grown wider as a result of the neoliberal policies and austerity measures. There are communities that are disproportionately affected by COVID-19.

### 22.3 Race and COVID-19

Racial bias in the age of COVID-19 has occurred in two forms. First, the United States and other pro-nationalistic governments politically stoked bias against people of Asian origins. Second, the virus amplified the structural inequalities and racial bias against Black Americans and other racial minorities in the United States.

The virus was scientifically named SARS-CoV-2, based on its similar structure to SARS-CoV. Although the virus could have popped up anywhere where the environment was conducive to interspecies transfer, SARS-CoV-2 originated in Wuhan, China. The US President Trump repeatedly referred to it as the “Chinese virus” or “Wuhan virus.”<sup>5</sup> This deliberate labeling was politically motivated to single out and blame the Chinese government and shield the Administration its inadequate response, and instead, it led to acts of aggression, and even physical violence, against people of Asian descent. In the eyes of the public, there was a strong association between the virus and East Asians. Cities like New York, Los Angeles, and rural states like Indiana have all reported incidents of discrimination and outright attacks on Asians due to the perception that they were directly responsible for the virus.<sup>6</sup> The singling out of Asians was not limited to America, but a global phenomenon.<sup>7</sup> Increases in racist rhetoric coincided with racially motivated attacks on East Asians in Europe, Africa, and Latin America, and against migrant workers in the Middle East and parts of Asia like Malaysia.

Second, racial bias in the United States is deeply seeded and plays out in terms of worse health outcomes for Black communities.<sup>8</sup> The situation with COVID-19 is no different. COVID-19 data collected at the national level from counties showed that the disease was more prevalent, and deadly, among Black and Hispanic communities. Even though Black Americans accounted for 22% of the United States, they had 52% of reported cases and 58% of deaths nationally.<sup>9</sup> A study from the Centers for Disease Control and Prevention (CDC) found that after adjusting for age, indigenous (Native) Americans and Blacks had a hospitalization rate five times that of white person, and Hispanic or Latino person four times, and attributed these differences to long-standing systemic health and social inequities.<sup>10</sup> The New York City Health Department created a report on infection and fatalities. Among Black

Americans, the death rate was 92.3 deaths per 100,000, Latin Americans had a death rate of 74.3, white Americans had a death rate of 45.2, and Asian Americans had a death rate of 34.5, in the lowest category.

Viruses do not discriminate on the basis of skin color, so why in the United States is there such disparity in mortality rates? The answer to this simple question is complex, and wrapped in layers of structural inequities and health disparities. The SDoH affects health outcomes. The living conditions for disadvantaged groups are but one reason. America has had a long-standing policy on residential segregation through *redlining*, a systematic policy put in place by city planners that made higher-valued properties inaccessible to underprivileged groups, either through high pricing or through outright refusal to sell to Black Americans and Hispanic people. The affordable housing available to Black communities was often poorly built and maintained, crowded and cramped, and included several generations sharing the same housing unit, factors that contributed to poor health outcomes.<sup>11–13</sup>

Living under such conditions makes it difficult for people to follow the rule of physical distancing recommended by CDC for COVID-19. With no green spaces and cramped quarters with many people living in high rises, the risk of exposure to COVID-19 increases, and especially vulnerable are the elderly family members and those with underlying conditions. At the same time, Blacks and Hispanics face disproportionately high risk because they are more likely to work in essential, low-paying jobs. Under the pandemic, people fulfilling such jobs have been designated as *essential workers* and face high risk of disease exposure through their employment.<sup>14, 15</sup>

On the flip side, racial minorities often do not have jobs that provide benefits such as paid parental leave, sick leave, or leave to care for elderly or ill family members. Black Americans and Hispanics are 7–13% less likely than their white counterparts to have access to these benefits.<sup>16</sup>

Racial minorities have typically faced significantly diminished access to paid parental leave, paid sick leave, and paid leave to care for sick family members. Compared to white individuals, African Americans faced diminished access to any of these accommodations by up to 7% across three models of calculation, with Hispanic individuals facing up to 13%. These disparities are long-standing and exist despite controlling for education and employment. Since health insurance in America is tied to employment, Black Americans and Hispanics usually have lower rates of health insurance and encounter difficulties in co-payments even with access through Medicaid.<sup>17</sup> In general, Black and Hispanic communities face discrimination in access health services, which are only magnified by the COVID-19 pandemic.

Unequal treatment of patients based on their race or ethnicity is well documented among health-care workers. In 2015, a study in Patient Education and Counseling found that patients from disadvantaged racial or ethnic backgrounds received less information from their doctors about treatment recommendations.<sup>18</sup> Princeton University found that white medical students and residents can hold onto false beliefs about biological difference between black and white patients, in doing so incorrectly report lower pain ratings for black patients. In simpler terms, students

and doctors with prejudices are less likely to believe black patients when they say they are in pain, and it affected their treatment recommendations negatively.<sup>19</sup> Bias like this has affected many medical fields. One of the most popular topics in public health today is the racial difference in maternal mortality. Black women are far more likely than their white counterparts to have negative outcomes, including death, during pregnancy. Racism in health care was specifically emphasized as a contributing factor.<sup>20</sup> In general, these types of actions and reactions can be classified under the umbrella term *implicit bias*. This refers to the prejudices and stereotypes that dictate an individual's actions without explicit intention to do so. And it did not stop when the pandemic hit.

A biotech data company, Rubix Life Sciences based in Boston, Massachusetts, reviewed recent billing information in several states and found that African Americans with symptoms like cough and fever were less likely to be given a test for the coronavirus.<sup>21</sup> Testing sites in historically black institutions also experienced greater delay in acquiring necessary testing equipment and protective gear. A heat map of Memphis of where coronavirus testing is taking place revealed that most screening was happening in predominantly white and well-off suburbs, and not the majority Black, lower-income neighborhoods.<sup>15, 21</sup> Disadvantaged racial groups are highly more likely to have comorbidities for coronavirus like hypertension, diabetes, HIV/AIDS, etc.

Diagnosis is the first step in receiving appropriate care for these patients. Identifying positive cases can encourage people to self-isolate and adhere to social distancing, keeping them from spreading the diseases if they end up being sent home. Delaying testing can allow for symptoms to worsen and result in hospitalization or even death, which could have been avoided.

## 22.4 Caste and COVID-19 in India

COVID-19 has created an unforeseen resurgence of caste-based discrimination, with fundamentalist using social distancing to re-enforce the idea of *untouchables* in Hinduism. The Hindu caste system India, and the current Bharatiya Janata Party (BJP) government steeped in religious ideology, has long ensured social segregation based on one's place in the hierarchy composed of four main groups—Brahmins, Kshatriyas, Vaishyas, and the Shudras—and the last group of Dalits or untouchables that number around 200 million. This group takes on the most menial and low-paying jobs, and for a variety of reasons, poverty being chief among them, are vulnerable to most diseases.<sup>22</sup>

In 2007, the Global Institute of Public Health and the Santhigiri Research Foundation found that women from the lower cast have greater likelihood of anemia, higher neonatal and infant mortality rates, and their children have a 30% higher likelihood of dying before their fifth birthday and only one in two have access to vaccinations.<sup>23, 24</sup> Another study reported that waiting time when visiting private doctors increased for those from lower social caste.<sup>25</sup> COVID-19 has resulted in social exclusion of Dalits from accessing government benefits or humanitarian aid,

and at the same time made them vulnerable to exposure given that they work essential jobs such as waste-pickers and sanitation workers. Since Dalits do not have the required government ID cards, they are unable to access any government benefits such as subsidies to food, access to public health-care services, or any other form of social protection. They were particularly affected by Prime Minister Modi's order of a nationwide lockdown on March 23 that gave only four hours' warning for these largely casual, migrant labors to pack up and leave urban centers.<sup>26</sup> Caste-based discrimination creates barriers to health services and increases risk of exposure, morbidity, and mortality.

## 22.5 Incarceration and COVID-19

America is known to have the largest prison population in the world, a problem called mass incarceration, referring not only to the total number of people in prison but also to the rate of imprisonment. Since 1970, the number of incarcerated people far outpaces population growth and crime, increasing 500% to 2.1–2.2 million people in jail and prisons today (655 incarcerated people per 100,000 people).<sup>27, 28</sup> The increase in incarceration is a result of changes in laws and policies, such as the “three-strikes” law, which automatically gives a person 25 years in prison for a third felony and prisoners who have been sentenced to life without parole.<sup>29, 30</sup>

Today one in nine people in prison are serving a life sentence, of which a third are sentenced to life without parole. Race plays an important role in incarceration, and research shows that Black citizens are six times more likely than white people to be incarcerated, and almost three times more likely than their Latino counterparts, who in turn are two times more likely to be incarcerated than white men.<sup>31</sup> According to a report by the Department of Justice, the population of prisoners aged 55 and older increased by 400% between 1993 and 2003, in part to longer sentences and in general an increase of admissions of older persons.

Mass incarceration has set up a perfect storm for a public health disaster such as COVID-19 in prisons. There are thousands of people kept in poorly ventilated confined space in close proximity with others and living conditions that create extreme stress on the body and mind. Despite being a closed facility, there is ample opportunity for exposure with prison staff entering and exiting daily, prisoners being transferred between facilities, and prisoners have little ability to maintain social distancing or safe hygienic practices. A federal prison in central Florida in February 2020 experienced an outbreak of Legionnaire's disease.<sup>32</sup> Ross Macdonald of the Riker's Island jail system described the happening as a “public health disaster unfolding before our eyes” to the *Guardian*, while reporting on 200 COVID-19 cases in 12 days in April.<sup>33</sup>

By June 6, there were 42,107 cases of COVID-19 and 510 deaths among 1,295,285 prisoners with a case rate of 3,251 per 100,000 prisoners.<sup>34</sup> The COVID-19 case rate for prisoners was 5.5 times higher than the US population case rate, a truly sobering statistic.<sup>35</sup> Women and minorities face particularly high risk since both groups have higher rates of chronic diseases. Correctional staff and their

families also share the high risks as they share the same environment and physical space. COVID-19 transmission is unlikely to be contained in US prisons without implementation of more effective policies that acknowledge responsibility, test, isolate and treat infected prisoners and their contacts, employ compassionate release for elderly and infirm prisoners, improve sanitation and provide personal protective equipment, and implement physical distancing.

## 22.6 Immigrants and COVID-19

In the middle of April, the US government made significant changes to the immigration system, including postponing immigration hearings, pausing deportation flight, suspending refugee admissions, and moving forward to blocking entry for asylum seekers and at the same time expelling anyone encountered at the border.<sup>36</sup> These measures were taken to protect the American economy from the impact of foreign workers on US labor market, but they also brought into sharp focus the intersection of immigration issues and public health policy.

According to data from the US Immigration and Customs Enforcement (ICE) Service as of July 1, more than 3,000 detainees have tested positive for COVID-19, that is, 25% of all detainees tested (11,828), or 13% of all detainees.<sup>37</sup> The largest number of positive cases (250) is from the Eloy Federal Contract Facility in Phoenix, Arizona. People living in detention centers face conditions similar to those in prisons, and cannot socially distance and have a limited access to soap.<sup>38</sup> They are also subject to deportation even though this can spread the virus. Those who are not under detention, but undocumented, often working in occupations such as agriculture or large meatpacking plants, are afraid to seek care when they are sick. Immigrants have been disproportionately affected by COVID-19.

Much of this information for medical care professionals is important with regard to understanding the pressures certain groups may be facing during clinical appointments. That is to say, keep in mind many patients may only be going to the doctor at the last possible moment because of financial needs or fears of how it may affect their immigration status. Furthermore, treatment plans should incorporate the likelihood of patients being able to return for an appointment or afford one. Another aspect is helping patients who are symptomatic or will understand the importance of isolating within the home, especially since it is known that people of color and immigrant groups tend to live with extended family. Some groups may have cultural healing practices or rely on religious prayer for healing, which may either expose them to more people or expose them to risk factors that worsen illnesses. Understanding the facts about different groups and cultures is what is known as cultural competence.<sup>39</sup>

While cultural competency is extremely important in setting patient care and understanding their risk factors with regard to infectious disease, this understanding is only halfway to what is required for highly sensitive patient groups. Medical care professionals risk losing patient contact when they fail to employ cultural humility.<sup>39</sup> This aspect takes competence one step further and acknowledges one's own



culture, and the moral equivalence of that culture to another. This is a lifelong learning responsibility for anyone working with a variety of people like health-care workers.

## 22.7 Economic Inequalities and COVID-19

The COVID-19 pandemic has highlighted the harsh reality of economic inequality within and between countries. Within countries, the chronic gap in wealth and employment surfaced as an acute problem. Those with financially secure jobs and savings were able to work from home and maintain social distancing compared with people who were living paycheck-to-paycheck or on daily wages through the informal sector found it difficult to pay rents and buy food.<sup>40</sup> People with money were able to create the physical distance between themselves and others, connect to others via Zoom, able to get food and other supplies delivered to their doors, and hoard necessities. But those without such affluence risked exposure through their jobs or lost their jobs altogether. The unemployment rate was higher for Black workers; 17.8% lost their jobs between February and April compared with 15.5% of white workers, with black women facing the largest losses of 18.8%.<sup>41</sup>

This scenario has played out in different parts of America prompting the US Congress to call for federally assisted income replacement, the Coronavirus AID, Relief, and Economic Security (CARES) ACT, which provides \$1200 per adult for individuals whose income was less than \$99,000 or up to \$3,400 for a family of four with children under 17 years old.<sup>42</sup> A total of \$293.4 billion to people who had filed taxes, but at the same time, the CARES Act handed out an almost equal amount, \$257.9 billion in 2020, in tax breaks and corporate losses to the country's wealthiest people and corporations.<sup>43</sup> The underlying inequalities continue to persist, and result in poorer health outcomes for the less affluent.<sup>44</sup>

The World Bank estimates that COVID-19 will push 71 million into extreme poverty of \$1.90 per day of earning.<sup>45</sup> Sub-Saharan Africa and South Asia will be hit hardest, and see large increases in the number of poor. Equally concerning are the marginally poor, who earn less than \$3.20 per day, and their numbers will increase to 176 million. The COVID-19 pandemic has laid bare the structural inequalities, inadequate health care, and the lack of social protections for the poor and exposed the social agenda that redefines the public good as helping the rich get richer.<sup>46</sup> The pro-growth policies, focused on GDP, have pushed aside the growing inequality, rising hunger, unaffordable health and housing costs, dismantled social safety nets, and promoted jobs that do not pay a living wage. According to Philip Alston, United Nations Special Rapporteur on extreme poverty and human rights, the coronavirus pandemic has only helped to lift the veil of a preexisting pandemic of poverty and inequality, and a political system that is designed by those in power to sustain and create wealth for themselves through an agenda of deregulation, privatization, and lower taxes for corporations and the wealthy. The dismantling of social safety nets and ecological devastation directly related to neoliberal policies will most likely create more threats to peoples' health and well-being.

## 22.8 Conclusion

COVID-19 has exacerbated the social determinants of health in the United States and around the world by creating job losses, food insecurity, housing instability, and unequal health care for communities of color, indigenous peoples, prisoners, immigrants, and other marginal and disenfranchised groups. Given the fragility of their lives, they have not been able to exercise the self-distancing and isolation required to prevent transmission. In the United States, Black communities have been disproportionately hit, but the reality is that all over the world those with limited resources and zero social safety have faced, and continue to experience, the brunt of COVID-19.

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## List of Abbreviations

CDC	Centers for Disease Control
CECC	Central Epidemic Command Center
COVID-19	Coronavirus disease
ICU	Intensive care unit
PPE	Personal protective equipment

### 23.1 Introduction

The philanthropist Bill Gates has referred to coronavirus disease (COVID-19) as a once-in-a-century pathogen that requires global cooperation for its containment.<sup>1</sup> With no availability of vaccines or widespread immunity among people, only public health measures can reduce transmission and control outbreaks.

Soon after the confirmation of human-to-human transmission of SARS-CoV-2, the Chinese authorities imposed a *cordon sanitaire*, a defined quarantine area from which those inside were not allowed to leave, around Wuhan and then Hubei province. In addition, the authorities ordered bans on public gatherings, compulsory stay-at-home policies, mandatory closures of schools and nonessential businesses, and face mask ordinances, among others.<sup>2</sup> Other neighboring countries had already imposed some of these measures along with testing, isolating positive cases, contact tracing, and quarantining those who had been exposed.

Nevertheless, from the time that the first case of COVID-19 was identified on December 8, 2019, to the time that the Chinese central government took full control of the outbreak, a total of 47 days had passed and the virus had spread far and wide both within China and across the globe. Multiple studies modeling the epidemic predicted that large overseas cities with transport links to China would become outbreak epicenters, unless substantial public health interventions at both the population and personal levels were implemented.

This chapter looks at the global spread of COVID-19 and the responses implemented by countries to control the pandemic. Although the world is still in the midst

of the COVID-19 pandemic, looking back over the early responses can provide insightful lessons about policy considerations, even as cases decline or disappear in some countries or increase and resurge in others.

## 23.2 East and Southeast Asian Response

The Chinese Center for Disease Control (CDC) informed the local offices of the World Health Organization on December 31, 2019, about pneumonia of unknown etiology. But since mid-December, the information had been percolating on Chinese social media<sup>3</sup> and Canadian-based disease tracking company, Blue Dot, had revealed news of the outbreak.<sup>4</sup> Neighboring Taiwan, 81 miles off the coast of mainland China, once learning of the official declaration, started to screen incoming passengers from Wuhan.<sup>5</sup> The Taiwanese government activated the Central Epidemic Command Center (CECC) that had been established in 2004 after the SARS epidemic. The CECC coordinated efforts by various ministries and managed the response to the entire crisis.

Since the outbreak occurred just before the Chinese Lunar New Year, a time during which millions of Chinese and Taiwanese travel for the holiday, the expectation was for Taiwan to have the second highest number of cases. However, the government's quick response with real-time alerts to classify travelers' infectious risks based on flight origin and travel history and case identification and isolation, quarantining of high-risk individuals, and regulating the pricing and availability of masks as well as fighting misinformation minimized the number of cases.<sup>6</sup>

Taiwan announced its first confirmed imported cases of COVID-19 on January 21, 2020.<sup>7</sup> By then, it made use of its established national disease surveillance and reporting system, as well as new location-based monitoring programs via cell phone geolocation.<sup>8</sup> The government also utilized a location-tracking phone-based application to monitor compliance with quarantine measures. Taiwanese citizens' unique health ID cards enabled doctors and hospitals to access online records allowing for easier access to records of individuals with COVID-19.<sup>9</sup> The hospitals prepared for surges, and the production of personal protective equipment was scaled up and face masks were made widely available to the public. All these measures meant that Taiwan, a country of 23 million citizens, could rely on less aggressive measures such as lockdowns and could allow the most economic activity to continue. It has reported only 480 cases and 7 deaths until today, August 10, 2020.<sup>10</sup>

Other countries in the region that had experienced the SARS outbreak of 2002 and 2003 rushed to implement nonpharmaceutical measures and active screening and quarantining of individuals entering from Wuhan. South Korea reported its first confirmed case of COVID-19 on January 20th (the same time as the first reported case from the United States). It had imposed screening measures on January 3 for individuals entering from Wuhan,<sup>11</sup> yet cases began to slowly rise over the coming months. On February 17, there were only 30 reported cases, but over the next 10 days, the cases grew exponentially, and by the end of February, there were nearly 3,000 COVID-19 cases in South Korea.<sup>12</sup>

The South Koreans, learning from their criticized MERS response in 2015 (cluster outbreak of 186 cases and 38 deaths due to five superspreaders),<sup>13</sup> acted quickly

to slow down transmission by expanding testing. The government in partnership with the private sector built hundreds of high-capacity screening clinics and 600 testing centers, with testing capacity reaching 15,000 to 20,000 tests per day. The nation of 51 million people also took a big data approach with contact mapping through credit card history and location from cell phone carriers. The authorities also pushed an intense, and mostly voluntary, social distancing campaign, but left most restaurants, stores, and social venues open for operation.

The Korean strategy included snuffing out clusters of disease outbreak through aggressive contact tracing and testing, housing positive cases in temporary isolation wards (separate from hospitals), monitoring their symptoms regularly through smartphone applications or by phone, and providing timely and accurate information to the public and health-care professionals about COVID-19.<sup>14</sup> Experience with past outbreaks provided that people wore masks and stayed at home without requiring government mandates. By the end of March, the pandemic was under control with fewer than 100 new cases per day and a total of 128 deaths. An outbreak connected to several nightclubs on May 12 was quickly brought under control. To date (October 3, 2020), South Korea reported 24,239 cases and 422 deaths compared to the United States with over 7.7 million cases and 215,278 deaths even though both countries reported their first case on the same day.

Post-SARS, other countries such as Thailand, Singapore, and Vietnam had also invested in their public health infrastructure. Thailand reported one of the first cases outside China (January 16), but its early adoption of facemasks combined with a robust health-care system and enforced lockdown in March (which was lifted in May) has kept cases to a minimum.<sup>15</sup> A popular tourist destination with millions of foreign visitors, Thailand has recorded only 3,600 cases and 59 deaths (October 3, 2020). It has imposed a strict 14-day quarantine period for all visitors. Other countries such as Cambodia and Laos in the Mekong River Basin also recorded few COVID-19 infections and deaths. Myanmar, however, saw a spike in confirmed cases from 336 reported in mid-July to 10,000 in September and over 20,000 as of October 3, 2020. However, deaths remain low at 471.

Vietnam was especially proactive, moving quickly to put into place screening and testing measures, quarantine centers for passengers coming in on international flights, initiating aggressive multilevel contact tracing, and informing people about COVID-19 through creative means such as songs and performances.<sup>16, 17</sup> Similar to Korea, the Vietnamese employed a cluster strategy of containing outbreaks and tracing contacts to the third degree (index case to those close proximity to index and those in contact with the close contact), and quarantining those that did not test positive for the virus in government-run centers and requiring self-isolation at home for 14 days. The extensive tracing was supplemented by possible commune-level lockdowns, and although Vietnam did eventually introduce a nationwide lockdown, it was relatively short-lived (April 1–15, but extended to 21 days in 28 out of 63 provinces).

Although the first confirmed case of COVID-19 was reported on January 23, Vietnam contained community transmission and has thus far (October 3, 2020) reported a total of 1,098 cases and 35 deaths until today. The majority of confirmed cases, nearly two-thirds, have been imported from China, Europe, and the United States.<sup>15</sup>



Singapore appeared initially well prepared, and established border screening and quarantine measures for all new arrivals.<sup>18</sup> The contact tracing was an intensive effort between multiple agencies that used activity mapping, analytic tools, and surveillance footage. The Singaporean economy remained open, and it seemed that the worst of the pandemic had been averted. However, in April, an outbreak of COVID-19 took hold among the 300,000 foreign workers living in overcrowded dormitories. The migrant workers were not allowed to leave and relied entirely on government support for food and water, communications, and entertainment. The country went into a lockdown on April 7 for nearly 2 months, but infection rates soared despite the high quality of health care.<sup>19</sup> Although deaths (27 in total) remained low, the paradox of high rate of COVID-19 infections (55,353 positive cases to date) highlights the vulnerabilities among migrant communities that have little control over their lives and living situation. Singapore started a phased lifting of restrictions on June 2, but remote working arrangements and keeping physical distance orders stay in effect. Migrant workers continue to remain in lockdown.

The Japanese government was initially criticized for its management of COVID-19 because passengers on the Diamond Princess cruise ship, floating off the coast of Yokohama city, contributed to the initial (but mild) wave of community spread. A larger surge occurred in late March, and cases were managed through 460 local public health centers (*hokenjo* in Japanese), which doubled as miniature centers of disease control.<sup>20</sup> The centers were strained, and became bottlenecks for testing, while designated hospitals brimmed with mild cases. In mid-April, the government declared a national state of emergency and shifted to restructure the strained health-care system into a more expansive network that included privately owned facilities and started to house mild and asymptomatic cases in converted hotels or ordered them to stay at home.

By May, Japan had flattened the curve and averted a full-blown health crisis compared to countries of similar demographics, like Italy (aging population), and economic development, like the United States.<sup>21</sup> It had managed to bring down transmission without large-scale testing or very restrictive social distancing by focusing on clusters of infection in gyms, pubs, live music venues, karaoke rooms, and similar types of establishments where people get together for extended periods of time. Japanese citizens complied voluntarily to wear masks and avoid large gatherings.

The public health responses to COVID-19 by Indonesia and the Philippines floundered and were delayed. Both countries continued to see new infections and deaths. Indonesia reported a total of 128,776 cases, an average of roughly 1500 new cases per day since mid-June, and 5765 deaths (August 10, 2020).<sup>22</sup> Philippines surpassed Indonesia in terms of total cases, 139,538 confirmed COVID-19 cases, and 2312 deaths. Over the past 2 weeks, new cases continued to grow exponentially with a jump from around 1500 cases at end July to over 6000 on August 9.<sup>23</sup> The pandemic has challenged the Philippines health-care infrastructure, and the country was included in the Global Humanitarian Response Plan together with 63 of the hardest hit countries in the South.<sup>24</sup>

### 23.3 Europe

On January 27, the WHO European Region and the European Center for Disease Prevention and Control (ECDC) introduced a surveillance system and asked countries to report confirmed and probable cases of COVID-19.<sup>25</sup> The overall strategic aim at the time was containment with a rapid identification of probable cases and contact tracing. The first case detected in France on January 19, followed by two cases on January 24, had direct links to Wuhan.<sup>26</sup> By February 21, 47 cases of COVID-19 were reported from 9 countries that included Belgium (1), Finland (1), France (12), Germany (16), Italy (3), Russia (2), Spain (2), Sweden (1), and the United Kingdom (UK) (9). Researchers observed transmission of infection taking place in two broad contexts: sporadic cases linked to travel from China and local community transmission in Europe.<sup>27</sup> Clustered outbreaks occurred in France/Spain (7 person cluster in Haute-Savoie and cases were detected in UK) and 14 cases from Bavaria, Germany, and the risk level of similar clusters and community transmission was raised from low to moderate, and then high.<sup>28</sup>

Although the Germans initially experienced a high rate of infection, they were able to slow down the transmission of the virus. They had developed the first diagnostic test for COVID-19<sup>29</sup> and started early testing for the virus, increased the capacity of hospitals to manage severe cases, and engaged in a transparent and scientific communications strategy. The German government at the federal and state levels undertook several measures such as social distancing, banning gatherings, wearing facemasks, and stay-at-home orders in some states. While these restrictive measures caused anger and frustration, and even protests, and were considered to impinge on basic rights, they contained the spread of the virus. By June, the UK had over 300,000 cases, over 100,000 more than Germany. More striking was the difference in the total deaths—46,526 deaths in the UK in comparison to 9268 deaths in Germany. An individual with COVID-19 was 6.5 times more likely to die in the UK than in Germany because of the delays in implementing public health policies.

The Germans were able to successfully handle the pandemic. At the forefront of medicine with a strong pharmaceutical industry, they had started early production of test kits and personal protective equipment (PPE). They introduced early lockdowns based on outbreaks, and followed up on positive cases and their contacts. As the country entered into a recession because of the lockdown, the government introduced an aid package of \$808 billion to mitigate the damage, which included support to further strengthen the health-care system, to provide help to small businesses and the self-employed, to provide state aid for companies, and to secure corporate debt at risk of defaulting.<sup>30</sup> A fresh domestic stimulus package worth \$146 billion was launched in June for 2020/2021<sup>31</sup> that included providing families with an extra \$336 per child.

In contrast, COVID-19 caught the Italians wholly unprepared. By mid-February, cases began to rapidly increase in northern regions of Italy and two deaths were recorded.<sup>32</sup> Similar to Wuhan, the Italian provinces in the northern region became the next epicenter, and cases rose from 3 to 50 to 800. On March 8, the Italian government closed public spaces and prohibited traveling to Lombardia, Emilia Romagna,

Piemonte, and Veneto. Commercial activities were closed aside from essential businesses. A nationwide lockdown was declared on March 9, and all flights were suspended. But these measures were introduced too late as 14 other countries in Europe confirmed their first cases seeded from travelers who visited Italy.

By March 19, the death toll in Italy surpassed that of China's totaling 4,634, and it was eventually 7.5 times more.<sup>33</sup> The health system was quickly saturated with cases, and faced major shortages of intensive care unit (ICU) beds, ventilators, and personal protective equipment.<sup>34</sup> The highly competent state-run health-care system, overwhelmed with cases, especially as flu season, was still ongoing, experienced overcrowding and disorder within and across hospitals resulting in high rates of transmission among medical personnel and patients. At one point, there were 900 deaths per day, and the horror stories of doctors being forced to choose who to treat and dramatic scenes of people lying on hospital floors circulated around the world.

A total of 35,216 deaths occurred in Italy, 87% in people over 70 years old,<sup>35</sup> and over 150 medical doctors<sup>36</sup> lost their lives. The crude mortality rate in Italy was 6–7%. The death rate was 58.3 per 100,000 population in Italy, almost six times that of Germany at 11.08 per 100,000 population and 10% less than the UK at 69.81 per 100,000 population.<sup>37</sup> The Italian government, however, did take several strategic steps to contain the unfolding crisis, including social distancing, mandatory face-masks, banning large gatherings, closure of nonessential commercial and retail businesses, and closure of schools and universities, among others.

The Italian government also passed a 25 billion Euros financial package, *Cura Italia*, of which 3.2 billion was used for strengthening the health-care infrastructure. New hospitals were built and the existing buildings were converted to house-infected cases. By early April, intensive care beds had doubled, and the departments for infection and respiratory disease received an influx of funding to purchase PPE. Community nurses were recruited to intensify testing and contact tracing. Any individual who tested positive, or who had come in contact with a positive case, was placed under self-isolation and home quarantine of 14 days. After nearly 70 days, Italy loosened its restrictions on May 4. But the Italian government's decentralized approach and bureaucratic red tape proved to be challenging in containing the outbreak and minimizing the deaths.

Following the spike of cases in Italy, Austria closed its border. But soon it confirmed two cases, tourists from Italy. Like many other countries in Europe, Austria did not shut down nonessential businesses until mid-March, and although it did not mandate wearing masks in public until April, it managed to contain the outbreak by a rigorous and punitive social distancing regime that fined people for breaking quarantine. The government set up a hotline to dispatch medical workers to test for COVID-19 at home, and also implemented a random testing policy to find presymptomatic and asymptomatic cases. As a result, there were only 22,439 infections and 724 deaths.<sup>38</sup> The mortality rate was 8.16 per 100,000 population.

France, like Germany, has a strong central government and advanced health-care system. But its death rate was 4.5 times higher than that of Germany even though it confirmed its first case around the same time. One reason for the difference was that the French government did not implement social distancing measures or ban large gatherings. Until early March, President Emmanuel Macron was still seen in large

gatherings, shaking hands, and kissing other colleagues, and even making public appearances in retirement homes.<sup>39</sup>

The French did not impose a lockdown until March 17, and failed to build their logistical capacity to promote mass testing.<sup>40</sup> Only 45 public laboratories were accredited, and there was a limited availability of reagents for RT-PCR testing. Instead of scaling up testing, authorities argued that systematic testing was not needed and only reversed their position in late March as a way to end the lockdown. Although France had an expert committee for scientific guidance, it proved ineffective in informing policy. The French also faced shortages of PPE, relying on China for both masks and testing kits.

The government introduced a series of laws to protect businesses, including a 300 billion euros loan program that included the protection of workers. It introduced “Operation Resilience” that used the French military to provide medical and logistical help, and created checkpoints to prevent people from defying lockdown order. But while these policies appeared to be heading in the right direction, the government decided to hold the first round of mayoral elections (a decision forced by political opponents of President Macron who wanted to take advantage of his rising unpopularity). However, the President postponed the second round given the low voter turnout and the severe losses incurred by his political party.<sup>41</sup>

On June 2, the government fully relaxed the lockdown measure. The French government, maintaining a reputation of being colorblind, refused to collect data by race, and it failed to acknowledge the disproportionate effect the pandemic had on its minority communities.<sup>42</sup> The politicization of COVID-19 crippled France’s ability to manage the public health crisis. Over 600,000 cases have been recorded in France and 32,299 deaths until October 3, 2020.

Greece has the second highest aging population in the European Union after Italy, and with years of economic hardship and austerity, it has a weak health-care system. However, the Greek government reacted swiftly to the threat of COVID-19, adopting an approach driven by science. Rather than promoting public messages that conflict with those of its own public health officials, Prime Minister Mitsotakis consulted with specialists from the University of Athens Medical School, the National Research and Technology Centre, and other institutions, and established a specialized task force that advised on policy and communicated with the public.<sup>43</sup> The emphasis on transparency quelled any backlash against socially disruptive measures that were introduced by the government. In addition, the government through a public–private partnership effectively managed its health resources, doubling its ICU capacity by the end of March.<sup>44</sup> It employed over 4000 new doctors and nurses, and spent an estimated \$5 billion per month.<sup>45</sup> As a result of its proactive interventions, Greece experienced only 6177 cases and 216 deaths.<sup>46</sup> It has opened up its economy and resumed tourism, a major source of revenue. Tourists entering Greece are tested for the virus, and depending on their results, they are either required to self-isolate or spend 14 days in supervised quarantine.<sup>47</sup>

Sweden was an outlier in comparison to its neighboring countries and never imposed a full lockdown, keeping businesses, restaurants, and most schools open throughout the pandemic. It did not officially prescribe policies of social distancing and the use of facemasks. Swedes naturally adopted preventative measures, such as

keeping their distances, limiting social interactions, refraining from forming crowds, and wearing masks. The approach resulted in a high death toll, nearly 6000 deaths or 567 deaths per million people compared to three times that of Denmark (166 deaths per million people) and 7 times that of Finland (59 deaths per million people) and Norway (47 deaths per million per million). The COVID-19 deaths per million in Sweden were closer to Italy than to its neighbors.<sup>1</sup> Sweden experienced an economic recession.

### 23.4 Oceania—Australia and New Zealand

Australia and New Zealand with two very different governments managed to successfully control the outbreak of SARS-CoV-2.<sup>48</sup> New Zealand reported its first case on February 26, and moved swiftly to shut down the country. Initially, it instigated shutting its borders to other nations, but a week later shut down all nonessential business and then went further implementing a level 4 lockdown, meaning that people could interact only within their household unit. The strategy was accompanied with text messages explaining what was expected from the individual, and accompanied by Facebook Live videos of the country's prime minister explaining the situation. As a result, New Zealand reported just over 1500 cases and only 22 COVID-19 deaths. The government of Prime Minister, Jacinda Ardern, also introduced a series of tax reforms that supported small businesses and protected individuals from losing their homes. In addition, in a symbolic gesture, Ardern and her ministers took a 20% cut in salaries.

The full lockdown allowed the government to get its systems up and running and to effectively manage testing and contact tracing, as well as surveillance.<sup>49</sup> The New Zealand response based on scientific evidence, leadership, and careful communication helped to slow down transmission and eliminate the virus.<sup>50</sup> On June 8, the country announced that it was COVID-19 free but it remains vulnerable to future outbreaks.

Australian leadership could not be more different than New Zealand, but it also managed to contain the COVID-19 outbreak by deferring to its scientists for guidance. As COVID-19 spread across the vast island, federal and state leaders from across the political spectrum coordinated their response rooted in scientific evidence. As early as March, Australia was possibly heading towards a public health disaster with cases rising exponentially and not enough testing.<sup>51</sup> The passengers on the Ruby Princess cruise liner, amounting to 700 COVID-19-positive cases (10% of total cases), were allowed to disembark and self-isolate despite exposure to COVID-19. The country also suffered from PPE shortages, with many health professionals unable to get enough materials for self-protection.<sup>52</sup>

But in the middle of March, the Australian government turned the tide and established a COVID-19 national cabinet to respond to the pandemic.<sup>53</sup> All states and territories met to agree and implement consistent policies on testing, social gatherings, visitor restrictions to long-term facilities, and quarantine period. Listening to health experts guiding policy, political leadership remained apolitical of the COVID-19 outbreak. Social distancing rules were put in place, and the government expanded access to telemedicine services to over 3 million patients.<sup>54</sup> Changes in hospital services,

including screening staff, patients, and visitors, as well as aggressive testing of those most at risk and effective communication prevented greater transmission.<sup>55</sup> As of October 3, a total of 27,173 cases of COVID-19 have been recorded with 895 deaths.<sup>56</sup>

### 23.5 The Americas

The only entry of a successful response in the Americas is Canada, which had experienced a localized SARS breakout in 2003 with 44 deaths.<sup>56</sup> This had pushed the government to invest in testing and surveillance infrastructure for any future pandemics, but even then Canadians were initially unprepared. They did not recommend social distancing or ban of large gatherings, facemasks, and other interventions until the first COVID-19 death.<sup>57</sup> Despite some delay in their response, the Canadian government implemented social distancing and lockdowns. Listening to the advice of health professionals, cross-partisan decisions and actions served to send a message of unity to the general public and reduce transmission.

However, Canada's public health system has three levels of jurisdiction—federal, provincial (10 provinces), and regional (3 territories). In a manner similar to the United States, where individual states determine the response, in Canada provinces and territories have the authority to determine strategies for containment, while the federal government focuses on international border closing, managing PPE supplies, testing kits, and ventilators. There was considerable cooperation between the federal and provincial governments including on policies related to social distancing, banning public gatherings, school and university closures, and closing of public spaces and nonessential businesses.<sup>58</sup>

Long-term care facilities for elderly struggled to contain the outbreak, and 81% of deaths occurred in these facilities.<sup>59</sup> Employees in elderly care worked in multiple facilities and were spreading the virus. The Canadian military was deployed to support facilities and contain transmission. Public health agencies hired extra people for testing and contact tracing, and the government introduced a new COVID-19 exposure mobile app. Masks were recommended in June and mandated in parts of Canada. By August 12, 2020, Canada reported a total of 120,844 cases and 9006 deaths. Currently, less than 300 new cases are being reported across the country unlike its neighbor the United States that has been recording over 50,000 new cases daily and 1,000 deaths.<sup>60</sup>

The US government response to the COVID-19 outbreak has been catastrophic, and President Trump's administration has left policymaking for the outbreak up to state governors. Often the federal government and some state governors have even downplayed the impact of the virus. As a result, the United States, which makes up 4% of the global population, has reported 26% of COVID-19 cases (5.4 million of the 20.8 million cases) and the highest number of deaths at nearly 170,000 (22% of total deaths) followed by Brazil at 104,263 (14%) deaths and India at 47,138 (6%) deaths (August 22, 2020).<sup>61</sup> However, as numbers have gone up globally, the United States proportion of cases has declined to 21.4% and deaths to 20.4% (October 3, 2020).

The US government initially ignored any warnings regarding the virus even though the administration was made aware of the outbreak on January 3.<sup>62</sup> The first

known case of COVID-19 was detected on January 19, a 35-year-old man in Snohomish County, Washington.<sup>63</sup> By February, there was evidence of person-to-person transmission,<sup>64</sup> but the cases were downplayed and President Trump repeatedly ignored warnings instead stating that the virus would disappear.<sup>65</sup> The CDC botched testing efforts, further delaying the ability to detect new cases.<sup>66</sup> State governors failed to recognize the severity of the crisis despite ample warning signs from Europe and Asia. Most officials delayed on providing transparent guidance based on scientific evidence and on introducing coherent public health policies of social distancing; banning large gatherings; wearing facemasks; and closing of schools, universities, and nonessential business. As the CDC advised and provided guidance to the Federal government and states on reducing transmission and flattening the curve, the responses remained inconsistent.<sup>67</sup>

By the third week of March, COVID-19 cases increased exponentially and cities such as New York and San Francisco scrambled to manage the outbreak. The epicenter of the pandemic had once again shifted, from China to Italy and now the United States. The pandemic exposed the fragility of some of the most marginalized American communities, including racial and ethnic inequities and economic disparities deeply rooted in decades of structural discrimination.<sup>68</sup> Five former CDC directors noted that America was behind the curve in containing the virus despite its considerable resources, scientific expertise, and state-of-the-art health infrastructure, and furthermore, simple behavioral interventions like wearing a mask had become far too politicized.<sup>69, 70</sup>

In March 2020, one of the earliest estimates of the impact of COVID-19 from the IHME (Institute of Health Metrics and Evaluation) projected “a total of 81,114 deaths (95% UI 38,242–162,106) from COVID-19 over the next 4 months in the US.”<sup>72</sup> As a result of many of the policy failures noted above, the number of deaths in the United States has already far exceeded this projection (170,000 on August 20, 2020). IHME’s latest (August 7, 2020) COVID-19 forecasts indicate that “the US will reach nearly 300,000 deaths by December 1, 2020.” The IHME issued simple and stark guidance along with this latest estimate, “if mask wearing in public increases to 95%, more than 66,000 lives could be saved.”<sup>73</sup>

In Brazil, President Bolsonaro’s response was similar to the US’s President Trump’s.<sup>71</sup> Even as cases rose, the government postponed issuing recommendations of physical distancing, wearing facemasks, banning social gatherings, closing schools and nonessential businesses, as well as regional lockdowns, and instead played down the virus, comparing it to seasonal flu. Many of these aforementioned public measures had been utilized in prior health emergencies such as H1N1 and the Zika virus, but had fallen out of favor with the current administration’s decentralized approach.<sup>72</sup>

President Bolsonaro’s rigid insistence that the virus posed no danger and later his belief in using hydroxychloroquine (unproven antimalarial drug as a remedy for COVID-19) resulted in the termination of his health minister, and resignation of the second within a month of taking on the job.<sup>73</sup> Testing remained low even as cases grew. Similar to the United States, where state governors and city mayors stepped in to mitigate the COVID-19 impact, in Brazil, the states and municipal governments stepped in to take up the mantle of responsibility.<sup>74</sup> In low-income

neighborhoods, known as favelas, transmission and mortality rates were higher, given that social distancing was a near impossible challenge.<sup>75</sup> Indigenous people and people of color were most affected with rates of transmission three times greater in poor neighborhoods compared to wealthy areas.<sup>76</sup> The first confirmed COVID-19 case was detected on February 26, and today (August 13), Brazil has the second highest number of cases after the United States at 3.1 million and reported over 100,000 deaths. Both countries were reporting an average of 55,000 new cases per day and over 1000 deaths per day.<sup>77</sup>

The Americas account for less than 10% of the global population, but have recorded 30% of COVID-19-related deaths<sup>78</sup> and 50% of cases (11.1 million).<sup>79</sup> The Pan American Health Organization Director noted that the COVID-19 pandemic revealed not only the structural deficiencies in the health sector resulting from years of inadequate public investment but also the inequalities around livelihoods.<sup>80</sup> Coupled with delayed initiatives, poor leadership, and misinformation campaigns that undermined the scientific realities, it should not be a surprise that the COVID-19 pandemic continues to rage in the Americas with the one exception of Canada, which manages to limit infections.<sup>81</sup>

## 23.6 Conclusion: Lessons Learned

While no government should be blamed for creating the COVID-19 pandemic, they should be scrutinized for how they responded in slowing down transmission and protecting the health of their people, including preventing excess mortality. The public health policies for containing the outbreak were the same, but the timing of their implementation varied across the world. Some countries imposed aggressive measures early on to contain and manage outbreaks, and others reacted slowly. The effect of travel restriction modestly slowed down viral transmission, by 3–5 days in China after the Wuhan lockdown.<sup>82</sup> But it had a marked effect at an international scale, reducing case importation by nearly 80% until mid-February. The authors concluded that travel bans and restrictions were not as effective as early detection, hand washing, self-isolation, and quarantine measures in mitigating the COVID-19 pandemic.

While this chapter did not cover the situation in western Asia, Middle East, Africa, and the Pacific, the elements of a successful response with regard to infections and deaths are evident in these regions as well. Listed below are the interventions shown to limit infection in the absence of vaccines and effective treatment.

### 1. **Early implementation of nonpharmaceutical public health measures:**

Given the airborne nature of COVID-19 transmission, outbreaks could only be limited by implementing measures such as physical (social) distancing, good hand hygiene, and facemasks. Banning large gatherings, closing schools, universities, public playground, and nonessential business, and mandating stay at home orders substantially reduced contact between people and helped to bring down the rate of transmission. Travel restrictions had a modest impact on reducing transmission, especially when community spread had already started.



2. **Testing, testing, testing! Isolating positive cases, contact tracing, and quarantining exposed individuals:** The importance of testing was central to containing COVID-19, especially clustered outbreaks that could turn into super-spreading events. Ongoing containment of viral transmission, especially as the next flu season approaches and restrictions are lifted, requires a robust testing strategy that includes positive individuals to self-isolate and their contacts to quarantine. A testing strategy should include both the RT-PCR and serological tests for antigens, and should focus on asymptomatic and presymptomatic carriers and priority populations such as the elderly, health-care workers, immunocompromised individuals or those with chronic conditions. Mass serological testing can also provide a prevalence estimate of COVID-19 in the population. The Brookings Institute and Washington University in St. Louis produced a computational simulation model to inform policy responses to COVID-19 called *Testing Responses Through Agent-Based Computation Epidemiology (TRACE)*<sup>82</sup> for the United States.
3. **Scientifically accurate and transparent decision-making and public communications by leadership:** Countries that made decisions based on medical and scientific evidence and communicated the true facts to their citizens managed to control the spread of the virus and minimize deaths. Governments that denied viral spread or built mistrust of their public health and medical officials fared much worse, resulting in greater confusion. They experienced a higher number of cases and, as a result, many more deaths.
4. **Well-resourced health infrastructure, including plans for pandemics:** Countries that had experienced the SARS outbreak were better prepared, including having a pandemic response plan coordinated across various government agencies. They were able to mobilize quickly and contain the outbreak. They had stockpiled PPE, maintained their health infrastructure (or in the case of China were able to quickly build as needed), and maintained sufficient investments in medical professionals and health-care workers. Governments who had been cutting health care and public services budgets did much worse, including those who had decimated their public health sector.
5. **Prioritizing the most at risk, which includes the poorest and most marginalized along with those who are vulnerable to the virus:** COVID-19 has brought out the stark inequalities embedded in today's globalized world. People with higher incomes and stable jobs were able to follow the public health recommendations, but those with lower incomes held essential jobs and were from ethnic and racial minorities. They were unable to keep physical distance, less informed about the pandemic, and often had preexisting conditions. As a result, they bore the brunt of exposure and mortality. Governments that prioritized a holistic approach and provided income support along with health services were able to contain the virus much quicker than those where there was an absence of universal, comprehensive health care, protection against job loss, and supplemental income.

COVID-19 has infected over 21 million people, and continues to rage in countries that never contained the virus and has resurged in some countries that ended community transmission because of international travel. This coronavirus may never go away. It is much more transmissible but not as deadly as its cousins—SARS and MERS—and outbreaks are going to continue to pop up. Even if it was eliminated from circulation among humans, the pathogen has successfully made the interspecies jump and could easily transmit back into humans from its animal host. Governments around the world have learned that they need to recognize their role in supporting health care and public health infrastructure, to put aside partisan differences in times of crisis in order not to sow confusion and distrust, to take care of their most disadvantaged citizenry in order to protect them as well as the population at large, and to heed the advice of experts and work in close collaboration with respective agencies in order to create coherence and consensus.

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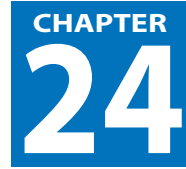
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# Looking Beyond the COVID-19 Pandemic



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## List of Abbreviations

COVID-19    Coronavirus disease

### 24.1 Introduction

Coronavirus disease (COVID-19) pandemic has overwhelmed countries, brought economies to a standstill, and forced people to sequester in their homes. With no vaccines or effective treatment available, interventions have focused on nonpharmaceutical methods along with testing, contact tracing, and quarantining. Some countries have managed to successfully control the initial unfolding of SARS-CoV-2 transmission, and developed strategies to mitigate the possibility of resurgence of infections. Others are still in midst of the first wave of the pandemic. COVID-19 is now part of diseases that infect people, and this chapter looks at the potential future of our world with COVID-19.

### 24.2 How Might the Pandemic End?

Theoretically, there are three possible scenarios characterizing how the coronavirus pandemic might end: one that is catastrophic, one that is the best possible scenario, and one that is in between the two.<sup>1, 2</sup>

The first scenario is based on building up herd immunity by allowing the disease to run its course through the population. This essentially means that few protective measures will be in place, and most people will become infected. Those who get infected and recover will begin to make up the immune population until hopefully, eventually, the virus will find no more viable hosts and fail to infect any more people. Herd immunity would only be possible if 70–90%<sup>3</sup> of the population became permanently immune.<sup>4</sup> This is the fastest way for the pandemic to come to a head and effectively eradicate the virus, but of course would be unspeakably disastrous for the human population and health systems worldwide.<sup>11</sup> Many people would die.



The second scenario is based on cooperation among leaders to control the spread of the virus through precise and aggressive containment measures. Comprehensive testing would be required in order to identify any and all cases, which are then placed under immediate isolation. Strong cooperation between leadership, full compliance of the public, and adequate resources would be a prerequisite to enforcing this level of containment.<sup>1</sup> This is an attractive strategy which could eventually shrink the magnitude of the coronavirus pandemic perhaps similar to the original SARS in 2003. Health policy expert Dr. Harvey Fineberg predicted it may take as little as 10 weeks to “crush the curve” with a forceful enough campaign.<sup>5</sup> However, given the exponential upward trend of outbreaks in the United States as well as the political, sociocultural, and economic climates that the pandemic was born into, this is astronomically unlikely to happen.

Finally, the third route is a strategy of mitigation until a vaccine comes. This is generally what is occurring around the world through various degrees of public health measures and the resulting daily number of cases. The summer and remaining months of 2020 are still described as part of the “first wave” in the United States.<sup>6</sup> The disease will remain circulating as long as containment measures are imperfect and as long as it takes for a vaccine to be made and distributed.

While there are still too many unknowns to accurately make predictions, the patterns of other coronaviruses and past pandemics may be considered for thinking ahead. Some researchers speculate transmission dynamics which depend on two unknown factors: immunity status after infection and seasonality of infection.

#### 24.2.1 *If Immunity is Permanent, then Covid-19 is a Relatively Brief and Intense Pandemic*

Kissler et al.<sup>7</sup> built a deterministic model of SARS-CoV-2 transmission dynamics with a focus on the United States and cross-immunity interactions between the 2019 virus and other coronaviruses.<sup>7</sup> Their projections consistently determined that given permanent immunity to COVID-19, the virus would cause a major outbreak and then effectively disappear in 5 or more years.<sup>1</sup> The WHO has found that most studies show that people generate antibodies to the virus after recovery. However, there is no evidence yet to determine whether or not antibodies to SARS-CoV-2 confer immunity to future infections.<sup>8</sup>

#### 24.2.2 *If Immunity is Temporary and not Permanent, then Covid-19 Enters Regular Circulation of Other Respiratory Infections*

In the case of temporary immunity, multiple sources point to the scenario of an initial wave of SARS-CoV-2 followed by the long-term seasonal flares much like the flu.<sup>1,4,9</sup> Kissler et al.<sup>7</sup> modeled different durations of temporary immunity leading to possible annual, biennial, or sporadic outbreak patterns. Based on other known coronaviruses, a duration of immunity of 40 weeks leads to an annual

pattern, while a longer 2-year immunity leads to biennial outbreaks.<sup>10</sup> Cross-immunity with the existing coronaviruses also plays a role in the duration of immunity.<sup>11</sup>

A Swedish modeling study also simulated different scenarios using data from the existing endemic coronaviruses.<sup>12</sup> Plausible model parameters show an initial phase in which northern and southern temperate and tropical regions see different patterns of circulation. After a few years, they predict SARS-CoV-2 will become a seasonal coronavirus with characteristic winter outbreaks. What determines seasonality? Infectious disease experts and biologists say that even for well-known diseases, it's not exactly clear.<sup>11</sup> Other researchers analyzed past pandemics since 1700 and did not discern any clear seasonal pattern for most. The 1968 pandemic (Hong Kong flu) was the only one with seasonality characterized by more winter-dominant outbreaks. Seven other pandemics in the past had an early peak, which waned until a second peak erupted about 6 months after the first.<sup>13</sup>

Some Russian scientists generated similar predictions when thinking from a virus–host perspective. They speculate that the virus will eventually become seasonal and endemic after a series of microevolutionary events during the initial wave. They paint a picture that perhaps one wintertime day in the future, a person will catch the virus, visit their doctor who will prescribe something like “covidol,” and recover in days.<sup>10</sup> While it is not an impossible future, only the virus and our collective actions will forecast how the pandemic will unfold.

## 24.3 The Future of COVID-19 and Dealing with the Years Ahead

### 24.3.1 Ongoing Mitigation

Every day of the pandemic, we learn from the mistakes and discoveries of others. It is vital that accurate information is shared widely in the public and in scientific communities. Much information is already constantly promulgated by health experts, public officials, and news outlets. Still, it is worth reinforcing how mitigation strategies are actually proving to work due to persistent objections and politicization of some of these measures.

Researchers and health officials acknowledge that an extended period of quarantine may not be realistic for many reasons. Moreover, a one-time quarantine might merely delay an inevitable peak.<sup>7, 14, 15</sup> Multiple sources conclude that a feasible strategy is *intermittent* social distancing as well as increasing critical care capacity.<sup>10, 14–16</sup> Decisions to increase or loosen distancing restrictions should be informed by ongoing and widespread testing, contact tracing, and other data collection. A short-term goal might be to balance economic activity without exceeding health-care capacities.<sup>7</sup> At the same time, development of vaccines and other interventions is an urgent priority. Research on serology would also be helpful to learn more about the long-term immunology and transmission dynamics of the virus.

For more information, see the following sections:

Ch. 21, 21.3	Vaccines, Vaccines in development for SARS-CoV-2
Ch. 18.2	Hospital Preparedness
Ch. 3.1, 3.2, 3.3	Transmission, Prevention, nonpharmaceutical interventions (NPIs)
Ch. 19	Diagnostics, Testing

The numbers evolve so rapidly, so it is important to keep a pulse on the local situation by regular testing. This might involve the implementation of systems in communities to streamline testing and reopening and restriction of activities. Without comprehensive testing, a significant percentage of transmission may occur unknowingly by asymptomatic individuals. Importantly, the use of cloth masks would help reduce asymptomatic transmission.<sup>17, 18</sup> Simple cloth masks with <30% efficacy (compared to  $\geq 70\%$  efficacy of medical-grade masks) have been proven to reduce the risk of infection and transmission of the virus.<sup>19</sup> Other preventative measures (see Chapter 3) should also be adopted.

A study published in March 2020 revealed early transmission in China.<sup>18</sup> Researchers used a very large pool of mobility data to build a dynamic networked population model, and subsequently made inferences about epidemiology of SARS-CoV-2. It was found that undocumented infections were the source of 79% of documented infections. Another modeling study used highly detailed mobility data to describe transmission dynamics in the Boston metropolitan area.<sup>16</sup> Aleta et al.<sup>16</sup> sought to calculate what percentage of the population would need to be quarantined in order to follow a proposed contact tracing and isolation strategy. If 50% of symptomatic infections were identified and 40% of their contacts were traced, then about 9% of the population would need to be quarantined at any given time. Researchers at Emory University generated a similar model with partial restoration of the economy based on testing.<sup>20</sup> This group investigated the role of serological testing in allowing seropositive individuals to be free of social distancing and act as “immunological shields.”

To be clear, these models were generated with limitations and imperfect parameters; thus, further confirmation is needed. However, the idea of selective quarantine alongside a semi-active economy may be worth exploring for a sustainable future.

### 24.3.2 Dealing with the Aftermath

This section addresses the period not only after the peak has passed, but in the event of successful eradication of the disease. The WHO has recommended actions to take on a national level in order to address the long-term health and social impact of a pandemic. These actions are multifaceted and subdivided into categories:

1. <b>Planning and coordination:</b> review lessons learned with the international community; replenish resources
2. <b>Situation monitoring and assessment:</b> evaluate the pandemic characteristics and situation monitoring and assessment tools for the next pandemic and other public health emergencies
3. <b>Reducing the spread of disease:</b> conduct a thorough evaluation of all interventions implemented
4. <b>Continuity of health-care provision:</b> evaluate the response of the health system to the pandemic, and share the lessons learned
5. <b>Communications:</b> publicly acknowledge contributions of all communities and sectors, and communicate the lessons learned, incorporate lessons learned into communications activities and planning for the next major public health crisis

Even without a vaccine, significant changes in individual behaviors such as hand washing and masks wearing and public policies can reduce disease transmission. Preventable diseases already cause huge losses of life. For example, on average, 400,000 people die each year from malaria; 1.5 million die from tuberculosis; and 140,000 children die from measles for which there is a vaccine. Since the virus selectively impacts the elderly and those with underlying chronic diseases, it is possible that with smart interventions, deaths in these groups can be averted in the future. COVID-19 unleashed an unprecedented, and rarely witnessed, rush of publications to mitigate its impact, share information on treatments, and find vaccines. In the midst of a lot of uncertainty, there is a lot that has been discovered and shared about COVID-19. As the pandemic evolves, this section and book will continue to evolve with it.

## 24.4 Conclusion

The COVID-19 pandemic has had devastating effects on people and economies. As of August 27, over 800,000 people had died. The economic effects to the world economies have also been devastating. It has resulted in one of the largest global recession in history with much of the world being locked down in quarantine.

It is expected that global contraction could reach greater than 2% in 2020. Although governments have recorded one of the largest financial fiscal packages in recorded history which to date is already greater than \$9 trillion, the impact of loss of jobs, livelihoods, and homes will have far-reaching consequences, including depression.

The coronavirus pandemic is also upending the US Presidential elections with conventions being held virtually to a significant amount of the votes to be done by mail.

It has changed the way campaigns will be conducted from limiting large campaign rallies to different tactics for fundraising. The COVID-19 response, deaths, and the economic effects are expected to have major impacts on the outcome of all aspects of the elections from the Presidential and control of the US Senate and House.

The COVID-19 pandemic has also changed the way patient care is delivered now and in the future. Telemedicine has grown an incredible 4000% during the pandemic and is expected that a significant number of health-care visits will continue to be virtual. All that is needed is a computer, tablet, or smartphone for two-way video interaction between providers and patients. In the United States, the laws allowing for reimbursement of telemedicine continue to evolve and the Congress and advocacy groups are asking private insurers to make telemedicine.

The COVID-19 pandemic is unfortunate, but its occurrence provides an opportunity to set up a different kind of world where health care can be delivered to all in a cost-effective manner, where mental health and well-being will become mainstream and part of health services, and where people will be the priority.

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