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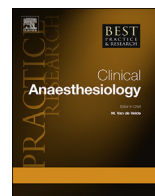
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Biology of COVID-19 and related viruses: Epidemiology, signs, symptoms, diagnosis, and treatment



Alan D. Kaye, MD, PhD, Professor, Provost, Vice Chancellor ^a,
 Elyse M. Cornett, PhD, Assistant Professor ^b,
 Kimberley C. Brondeel, Medical Student ^c,
 Zachary I. Lerner, Medical Student ^d,
 Haley E. Knight, Medical Student ^e,
 Abigail Erwin, Medical School Student ^d,
 Karina Charipova, BS ^f, Kyle L. Gress, BS ^f, Ivan Urits, MD ^g,
 Richard D. Urman, MD, Associate Professor ^{h,*},
 Charles J. Fox, MD, Professor and Chairman ^b,
 Christopher G. Kevil, PhD, Professor, Vice Chancellor ^a

^a LSU Health Shreveport, 1501 Kings Highway, Shreveport LA 71103, USA

^b Department of Anesthesiology, LSU Health Shreveport, 1501 Kings Highway, Shreveport LA 71103, USA

^c University of Texas Medical Branch, 301 University Blvd, Galveston TX 77555, USA

^d LSU Health Sciences Center New Orleans, 1901 Perdido Street, New Orleans, LA 70112, USA

^e Louisiana State University Health Sciences Center, New Orleans, LA, 70112, USA

^f Georgetown University School of Medicine, Washington, D.C., 20007, USA

^g Department of Anesthesiology, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

^h Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115, USA

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Coronaviruses belong to the family *Coronaviridae* order *Nidovirales* and are known causes of respiratory and intestinal disease in various mammalian and avian species. Species of coronaviruses known to infect humans are referred to as human coronaviruses (HCoVs). While traditionally, HCoVs have been a significant cause

* Corresponding author.

E-mail addresses: akaye@lsuhsc.edu (A.D. Kaye), ecorne@lsuhsc.edu (E.M. Cornett), kcbronde@utmb.edu (K.C. Brondeel), zlerne@lsuhsc.edu (Z.I. Lerner), hknig1@lsuhsc.edu (H.E. Knight), aerwi1@lsuhsc.edu (A. Erwin), kc1032@georgetown.edu (K. Charipova), klg93@georgetown.edu (K.L. Gress), ivanurits@gmail.com (I. Urits), rurman@bwh.harvard.edu (R.D. Urman), cfox1@lsuhsc.edu (C.J. Fox), ckevil@lsuhsc.edu (C.G. Kevil).

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of the common cold, more recently, emergent viruses, including severe acute respiratory syndrome coronavirus (SARS-CoV-2) has caused a global pandemic. Here, we discuss coronavirus disease (COVID-19) biology, pathology, epidemiology, signs and symptoms, diagnosis, treatment, and recent clinical trials involving promising treatments.

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Introduction

Coronaviruses are a family of positive-sense, enveloped RNA viruses that cause various illnesses in mammals and birds [1]. These viruses represent the largest group within the *Nidovirales* order, which comprises the families *Coronaviridae*, *Arteriviridae*, *Mesoniviridae*, and *Roniviridae*. Structurally, coronaviruses are characterized by an unusually large RNA genome and club-like glycoprotein spikes that project from the surface of its envelope [2]. These spikes result in a characteristic ultrastructure appearance resembling the solar corona, giving rise to the name “coronavirus” [1,3]. Although they were first identified in 1965, human coronaviruses (HCoV) have recently gained notoriety due to their role in global outbreaks [4,5].

The human coronaviruses HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 typically cause mild upper respiratory infection and are responsible for approximately 15%–30% of all cases of the common cold in adults and children [6,7]. Coronaviruses also cause a range of respiratory and gastrointestinal (GI) infections in animals, affecting pigs, cows, mice, bats, and chickens with varying degrees of severity [2]. Although most coronavirus strains result in mild, self-limited upper respiratory disease in humans, three global outbreaks of severe disease due to novel coronaviruses have occurred in the twenty-first century. Severe acute respiratory syndrome (SARS) was first identified in Guangdong province, China, in 2002, resulting in over 8000 cases and 744 deaths worldwide before being contained in 2003. Middle East respiratory syndrome (MERS) was diagnosed in Saudi Arabia in 2012, ultimately spreading globally and leading to 2494 cases and 858 deaths [8]. Most recently, SARS-CoV-2, the novel coronavirus responsible for coronavirus disease-2019 (COVID-19), was identified in Wuhan, China, in January 2020 [9]. As of October 2020, the resulting global pandemic has caused over 33,249,000 confirmed infections and 1,000,040 deaths [10].

Early symptoms of COVID-19 infection include fatigue, fever, dry cough, and anosmia. Approximately 80% of cases are mild and self-limited, primarily affecting the upper airway with limited involvement of the lungs. Severe infection, characterized by dyspnea, tachypnea, hypoxemia, cardiovascular sequelae, and extensive lung disease, occurs in 15% of cases. Critical infection, characterized by respiratory failure, septic shock, and multisystem organ dysfunction, and often complicated by acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulopathy (DIC), occurs in 5% of cases [11–13]. The estimated case fatality rate is 2% overall, and 49% among critically ill patients [14]. Patients with comorbid illness, including hypertension, diabetes mellitus, cardiovascular disease, lung disease, and cerebrovascular disease, have increased risk for poor outcomes due to COVID-19 [15]. Elderly patients also experience increased morbidity and mortality due to COVID-19 infection [11,16].

On October 22, 2020, the FDA approved the antiviral drug, remdesivir, to treat COVID-19 in patients 12 years and older who are hospitalized [17,18]. Furthermore, as of November 2020, two pharmaceutical companies have developed promising COVID-19 vaccines that are up to 95% effective [19,20]. In addition to these treatments, the management of COVID-19 is primarily supportive. Supplemental oxygen is the initial treatment for respiratory impairment, while patients with continued respiratory distress or respiratory failure may require noninvasive positive pressure ventilation and mechanical ventilation [21]. Corticosteroids have also shown promise in the management of COVID-19 [22,23].

In this review, we first discuss coronaviruses' molecular biology, including the viral structure and replication process. Next, we discuss the pathology of coronavirus infection and SARS-CoV-2, highlighting the role of the angiotensin-converting enzyme 2 (ACE2) receptor in viral entry to host cells.

Epidemiology of the COVID-19 pandemic is examined, including a timeline of the outbreak, an account of the populations that have been affected, and a discussion of risk factors for infection and subsequent poor outcome. Signs and symptoms of COVID-19 infection are also reviewed. Finally, we outline current methodologies in diagnosing and treating COVID-19 and highlight recent clinical studies that continue to advance the body of knowledge in managing this unprecedented disease.

Biology of coronaviruses

Coronaviruses are enveloped, positive-strand RNA viruses with genomes of up to 33.5 kilobases (kb) considered the largest among all RNA viruses [24,25]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), similar to other coronaviruses, is characterized by trimeric S glycoproteins located on a pleomorphic (round or oval) outer membrane [26,27]. The viral envelope comprises structural proteins M and E, while the genome is coupled with protein N [27]. The complex structure of the virus is thought to contribute to its ability to survive in aerosols for up to 3 h [27]. The spike-like S proteins project from the virus's surface and play an integral role in allowing the virus to bind to the ACE2 receptor, an intermembrane receptor prevalent on epithelial cells and type II pneumocytes in the lower respiratory tract (LRT) [25,26]. Functional studies have also demonstrated that SARS-CoV-2 S proteins utilize transmembrane serine protease 2 in addition to ACE2 for entry into the host cell [28]. Following binding through the receptor-binding domain (RBD) of the S glycoprotein, the S protein undergoes large-scale conformational changes that allow the virus to endocytose into the cell cytoplasm where it undergoes replication [25,26]. Like other coronaviruses, SARS-CoV-2 replicates using a mechanism of continuous RNA synthesis but conducts transcription through a discontinuous process unique in the RNA virus world and is a characterizing feature of the *Nidovirales* order [24]. Discontinuous transcription in the coronavirus is regulated by multiple factors, including the essential coronavirus N protein RNA chaperone, which maximizes transcription efficiency [24]. Alongside the proofreading machinery encoded by coronaviruses, the discontinuous transcription process facilitates the upkeep of the large genome [24].

Recognition of the ACE2 receptor by SARS-CoV-2 and the subsequent conformational changes in the S protein that promote viral-host cell membrane fusion are critical steps to infection [28]. Given the S protein's importance, its structure and interactions with host receptors represent a popular niche for research to develop antivirals and ultimately, a vaccine [28]. The analysis of sequenced SARS-CoV-2 genomes has demonstrated that mutations in the S protein have contributed to creating predominant virus clades in various parts of the world, such as the D614G mutation notably found in Europe [29]. Certain regions of the S protein have also enabled the differentiation of SARS-CoV-2 from SARS-CoV and improved the specificity of serologic testing [30]. Through the function of the S protein, SARS-CoV-2 is believed to replicate in the olfactory epithelium of the nasal cavity and spread along the tracts of the airway [31]. It is this initial locus of replication that is thought to explain the clinical manifestation of loss of smell experienced by some individuals [31]. In more severe cases, SARS-CoV-2 travels along the airway to the lungs to cause severe pulmonary disease with potential systemic sequelae such as neurological symptoms and multi-tissue dysfunction [31,32]. Wide tissue dissemination of the virus is believed to result from the presence of targets, in the form of the ACE2 receptor, on various tissue types, including the cardiovascular system, GI tract, and central nervous system [27]. Among the systemic effects of COVID-19, it has been recently suggested that CD169+ macrophages located in the spleen and lymph nodes can serve as viral carriers that can maintain viral load and facilitate tissue dissemination [27]. Some investigators have suggested that the generation of the S1 protein by the virus and release of this protein into circulation may limit the severity of infection and tissue damage to maintain adequate transmission rates [33].

Mutations in the sequences coding for S glycoprotein and other proteins in the structure of SARS-CoV-2 are believed to at least partly explain the high infectivity and pathogenesis of the virus [27]. Mutations in the spike protein's RBD have enabled the virus to bind to human, cat, and ferret ACE2 receptors with significantly higher affinity than SARS-CoV-1 [27]. Studies have yet to fully resolve whether mutations that result in lineage changes such as those that have led to different predominant clades even between the East and West Coast of the USA have impacted viral pathogenesis or overall fitness [27]. Future investigation of these mutations is also needed to discern how SARS-CoV-2 adapts

to not only various climates but also fits in with endemic viruses and parasites such as malaria, tuberculosis, and HIV [27]. This kind of phylogenetic analysis has the potential for not only tracing infection routes but also guiding treatment development [28]. The viral replication and livelihood of SARS-CoV-2 is promoted further by nonstructural protein 1 (nsp 1), which allows the virus to dominate the host's genomic machinery that enables it to generate progeny at the expense of the host [27]. This pathogenic factor also inhibits the host's ability to express type 1 interferons (IFN-1), leading to the subsequent decreased expression of major histocompatibility complex 1, reduced antigen presentation, and suboptimal T cell response by the host [27]. The host's antiviral resistance is further subverted by the action of viral proteins that target ubiquitin ligases and dysregulate defensive signaling [27]. The analysis of the affinity of SARS-CoV-2 products for the components of the antiviral defense of the host has demonstrated that the presence of specific HLA alleles has the potential to mediate antiviral response [27]. These studies have hypothesized that a lack of the HLA-B*46:01 allele may predispose individuals to increased vulnerability to infection, while the presence of HLA-B*15:03 may induce cross-protective T-cell immunity against SARS-CoV-2 and other coronaviruses [27]. Furthermore, compared to noncritically hospitalized COVID-19 patients, ICU patients with severe COVID-19 disease showed a reduced expression of mHLA-DR on circulating CD14+ monocytes at ICU admission, suggesting dysfunctions immune response in these patients [34].

Pathology

While coronaviruses have long been known to cause a variety of severe illnesses in livestock and other animals, prior to the SARS-CoV outbreak in 2002, coronaviruses were thought to cause only self-limited infections in humans [25]. Historically, coronaviruses were accepted as endemic in the human population, having low virulence and causing 15%–30% of all annual respiratory tract infections [24,25]. The dissimilarity between the severe disease states caused by coronaviruses in nonhuman species and the mild illnesses caused by HCoVs has conventionally been thought to relate to their differential tolerance to genetic variability [25]. For instance, it has been hypothesized that the minimal sequence divergence of HCoV-229E explains its inability to cross the species barrier and infect mice [25]. The emergence of SARS-CoV not only dispelled the belief that coronaviruses could not cause life-threatening diseases in humans but also demonstrated transmission of the virus from bats to humans [25]. SARS-CoV-1, which over the span of the 2002–2003 epidemic was linked to over 8000 cases and over 700 deaths as well as billions of dollars lost in economic activity, is thought to have originated in Chinese horseshoe bats [25]. Bat SARS-related CoVs were found to be more similar to SARS-CoV than any other viruses to date and were additionally found to utilize the same ACE2 receptor known to be used by HCoVs [25]. As most HCoVs, infection with SARS-CoV resulted in more severe illness and higher mortality rates in comorbid and elderly patients [25]. Interestingly, the age-dependent increase in severity seen in humans infected with SARS-CoV has been replicated by studies analyzing the disease course in rodents infected with adapted forms of the virus [25]. Although mapping of SARS-CoV-1 showed that it spread to over 25 countries, the transmission of the virus was relatively inefficient with spread occurring only through direct contact after onset of illness [25,27]. The virus was largely contained through quarantining with only a small number of known cases being thought to have occurred after the outbreak was deemed controlled in June 2003 [25]. A similarly contained outbreak of coronavirus MERS-CoV took place in 2012, wherein zoonotic infection was transmitted vertically from camels to humans [27]. While the nearly 2500 infected individuals and over 868 fatalities associated with MERS are not to be discounted; to date, these infection events remain localized to the Middle East due to relatively low rates of transmission [27].

SARS-CoV-2 causes a respiratory illness now referred to as coronavirus disease-2019 (COVID-19). From its emergence in December 2019 at its epicenter in Wuhan, China, the infectious agent spread quickly to all parts of the globe and was subsequently declared a global pandemic by the World Health Organization (WHO) on March 11, 2020 [26,29]. The rapid spread of infection from SARS-CoV-2 quickly drew comparisons to the new strain of H1N1 influenza that emerged in 1918 and is colloquially known as the “Spanish flu” [27]. As of October 1, 2020, the virus has resulted in over 33.5 million cases and over 1 million deaths with significantly worse outcomes and higher mortality in the elderly [32,35]. While the mechanism by which older patients suffer more severe disease is still under investigation, it has

been proposed that higher levels of cellular senescence may contribute to the development of cytokine storm, excessive inflammatory reaction, increased tissue damage, and multi-tissue dysfunction in these patients [32]. Prior to the implementation of any public health interventions, the basic reproduction number of SARS-CoV-2 was estimated to be as high as 5.7, meaning that each infected individual had the potential to transmit the disease to as many as 5 to 6 new individuals [27].

While the pathophysiology is complex and not fully understood at the time of this writing, like SARS-CoV-1, SARS-CoV-2 is thought to primarily target the lung's epithelial cells, inducing the production of proinflammatory cytokines and a concurrent reduction in T-lymphocyte response [25]. The virus has been shown to share approximately 80% of its sequence identity with its predecessor, SARS-CoV, causing significant cross-reactivity in serological testing [27,30]. Although the cross-reactivity of SARS-CoV-2 with SARS-CoV-1 has given rise to obstacles when it comes to testing, it also enables cross-neutralizing antibodies to SARS-CoV-1 to target SARS-CoV-2, perform opsonization, and clear the virus [27]. Recent studies have demonstrated that patients who develop only mild symptoms, the clearing of COVID-19, can occur within ten days following symptom onset through the action of alveolar macrophages that resolve inflammation within the lungs and propagate tissue remodeling following the initial inflammatory phase [27]. A recent study in New York City involving 30,000 patients reported significant viral neutralization ability, which correlated with their antibody titer levels [36]. Furthermore, long-term immunity may occur in patients who have recovered from the virus [37].

Hopefully, future studies will be able to shed light on SARS-CoV-2 transmission and the development of immunity, which helps to not only answer these questions but also to ultimately curb the spread of this deadly infection.

Epidemiology

Timeline

SARS-CoV-2 first emerged in Wuhan, China, at the end of December 2019 as a cluster of atypical pneumonia cases. On January 11, 2020, China reported the first death caused by the novel coronavirus [38]. By January 21, 2020, the United States confirmed the first case of the virus with a 35-year-old previously healthy man that presented with a history of cough and subjective fever after returning from a visit to family in Wuhan, China, on January 15, 2020 [5]. On January 30, 2020, with increasing evidence of human-to-human transmission outside of China, the WHO declared the novel coronavirus a Public Health Emergency of International Concern. On March 11, 2020, the WHO officially upgraded the COVID-19 state of emergency to pandemic [38].

As of September 30, 2020, there have been 33,502,430 confirmed cases of COVID-19 worldwide, with 1,004,421 deaths reported to the WHO. At the time of writing, the United States makes up greater than 10 million of the confirmed cases, with over 250,000 deaths to date. Within the U.S., the peak of COVID-19-related deaths occurred in late April to May, with the peak of incidence occurring in late July to early August, and a third surge currently underway [39]. America is still in the leading three countries for new daily cases, with 32,688 cases reported in the last 24 h. The Region of the Americas remains the most affected WHO Region, accounting for 50% of all reported cases and 55% of deaths [40].

Diagnostic criteria and epidemiological breakdown

The WHO categorizes COVID-19 patients into mild, moderate, severe, and critical disease. Mild disease is defined by patients that meet clinical and epidemiological criteria without the evidence of viral pneumonia or hypoxia. Moderate disease is characterized by the evidence of pneumonia. Severe disease is defined by severe pneumonia with a respiratory rate >30 breaths/min or the evidence of severe respiratory distress. Critical disease is defined by severe pneumonia complicated by the onset of ARDS, sepsis, or septic shock [41]. Most people infected with COVID-19 will develop only mild-moderate symptoms (80.9%), with 13.8% of people developing severe disease and 5% developing critical disease [42].

Demographic distribution of COVID-19 in the United States

The CDC reports of demographic trends of COVID-19 in the United States are limited by reports that failed to include race/ethnicity data. Reported death data and reported incidence data contained racial/ethnicity information, only 82% and 51% of the time. Black, Non-Hispanic Americans account for 13.4% of the population but account for 18.2% of reported COVID-19 cases. Hispanic/Latino Americans account for 18.5% of the population but account for 29.1% of cases. Reported deaths follow a similar trend, but notably, Hispanic/Latino Americans trend in reported deaths is more closely matched to their representation within the population at 16.5% [43,44]. The CDC has reported 76.3% of cases to occur among people aged 18–64 years, with 79.2% of deaths occurring outside of this age range, in those 65 years and older. When broken down by gender, case incidence is slightly higher in female subjects though death reports are more highly reported in male subjects [43].

Epidemiological risk factors

An epidemiological study ($n = 72,314$) conducted early in the pandemic found that age, male gender, and the presence of comorbidities are factors of an increased risk for severe Covid-19-related disease and/or mortality [42]. When compared to non-severe COVID-19 patients, the development of severe illness or admission to ICU is more likely in patients who suffer from one or more comorbidities in the descending order of odds ratio strength: chronic obstructive pulmonary disease, diabetes, cerebrovascular disease, coronary heart disease, hypertension, and malignancy [45].

Smoking history is also a risk factor associated with severe ICU cases of COVID-19 [45]. According to the most recent analysis of smoking status in COVID-19 patients, while current smokers and those with the evidence of smoking history are more likely to develop severe or critical COVID-19 and the need for mechanical ventilation, only smoking history is significantly associated with increased in-hospital mortality [46].

Obesity in people <60 years is an independent poor prognostic epidemiological risk factor. In a study by Lighter et al. that stratified patient age and BMI, the rate of hospitalization in young patients with a BMI >30 was 2.0 times more likely. ICU admission was also found to be increased at a rate of 1.8 and 3.6 in young patients with BMIs 30–34 and ≥ 35 , respectively [47]. In ICU patients who required invasive mechanical ventilation (IMV), obesity was found to be more prevalent in COVID-19-positive patients as compared to non-COVID-infected ICU controls [48]. The most recently available national data show that obesity in the United States among adults was 42.4% in 2017–2018 [49]. With poor prognostic outcomes demonstrated in obese COVID-19-positive patients, a significant portion of the United States population can be considered high risk.

Transmission and implications for PPE and quarantine guidelines

The SARS-CoV-2 virus is a member of the coronavirus family that causes respiratory disease. The virus primarily spreads through respiratory droplets but has also been shown experimentally to have sustained viability on surfaces such as plastic and stainless steel for up to 72 h, on cardboard for up to 24 h, and copper surfaces for up to 4 h [50]. Spread through aerosols has been confirmed by the CDC [51]. In a small study of confirmed COVID-19-isolated patients, viral RNA was found on environmental surfaces related to the deposition of droplets by airflow. The virus was also found in toilet bowl and sink samples suggesting viral shedding in the stool and can be measured in sewage wastewater [52].

Coughing and sneezing generate large respiratory droplets ($>5 \mu\text{m}$) where exhaling and regular talking generate small aerosols ($\leq 5 \mu\text{m}$) [53]. In a study of facemask efficacy in reducing spread in respiratory viruses, coronavirus was found to only be detectable in samples of respiratory droplets and aerosols collected from patients not wearing facemask coverings [54]. Because the previous SARS-CoV-1 virus could be detected in patient tears, and the current SARS-CoV-2 is transmitted through fomites and droplets that could contact the eyes, eyewear protection necessary for spread prevention [55,56].

The pandemic's rapid global spread is partially attributed to asymptomatic transmitters of disease that would go on to develop symptoms after creating clusters of outbreaks [57]. Early symptomatic presentation trends lead research to suggest a median incubation period of approximately five days

[58,59]. A recent study asserts that the incubation period is longer, lasting nearly eight days with 10% of patients demonstrating the first onset of symptoms after 14 days [60]. This is a public health concern as the current quarantine guidelines suggest only a 14-day quarantine in those with suspected exposure.

Signs and symptoms

Typical and atypical signs and symptoms of COVID-19 infection

Although asymptomatic transmission of COVID-19 occurs at a high rate, an entirely asymptomatic course is unlikely, totaling up to as few as 1% of cases [42]. The asymptomatic incubation period is better thought of as a presymptomatic period. Because the WHO classification of disease starts with clinical presentation, and symptomology can take more than 14 days to present, prompt recognition of signs and symptoms is paramount to halt the spread of the disease [41,60]. The most reported and reliable presenting features of COVID-19 infection are fever and cough [61–63]. Other frequent presenting symptoms include fatigue, myalgia, and dyspnea. Atypical symptoms of infection include chills, G.I. upset, and neurological changes [61].

Fever and dyspnea

A meta-analysis compared clinical features and outcomes of COVID-19 patients between those classified as severe (ICU) and nonsevere (non-ICU). Fever and dyspnea were significantly associated with severe disease, though increased fever >39 °C was not statistically significant between groups. Other symptoms such as cough, nausea, headache, sore throat, diarrhea, myalgia, and fatigue were not statistically favored by either group [45]. Consistent with these findings, Xiang et al. found dyspnea to be the most valuable prognostic indicator of severe pathology, regardless of independent patient risk factors, high fever, headache, and diarrhea as statistically insignificant with regard to prognosis [64].

Chills

Chills are not a highly prevalent manifestation of COVID-19 infection, but when stratified against other clinical features and lab findings, they show strong positive correlations with diagnostic markers of infection. Chills demonstrate a strong negative correlation to age and lymphopenia, which are associated with worse clinical outcomes [61]. Limited data have been collected regarding chills as a feature of disease. Still, these data suggest chills to be helpful in diagnosis and as an excellent prognostic indicator of disease course.

Gastrointestinal manifestations

Gastrointestinal (GI) symptoms were overlooked in early studies due to low prevalence, but recent data show prevalence can range from 5% to 61% [61,65]. The ACE2 receptor is a known receptor for entry into host cells in both SARS-CoV-1 and SARS-CoV-2. High expression of this receptor has been detected in cells of the lungs and intestinal mucosa [66,67]. Viral shedding has been detected in fecal samples and on objects such as toilets and sinks that encounter fecal matter, lending credence to the plausibility of fecal-oral transmission [52,68]. Though most studies have found diarrhea and other GI symptomatology to be insignificant with regard to disease severity, one meta-analysis demonstrated the presence of GI symptoms in 17.6% of patients with a higher prevalence among severe COVID-19 patients, and a study of pediatric patients found GI symptom prevalence in 43% of severe cases [63,68].

Neurological manifestations

Data on neurological pathology in COVID-19 patients is not extensive because it was not initially considered a manifestation of the disease. In February, a study of hospitalized patients showed 36.4% of patients had nervous system manifestations, including CNS, PNS, and skeletal muscle injury. Patients with severe infection (41%) were more likely to develop neurological manifestations, and some of these

patients presented without typical symptoms of fever, cough, anorexia, and diarrhea [69]. The expression of ACE2 is found in several places in the body, and its expression within the nervous system may lead to neurological manifestations as similarly proposed within the GI system [69]. In patients with mild disease, impaired sense of taste and smell is reported in 64%–88% [70,71]. See Fig. 1.

Presentation in children

The presentation of COVID-19 in children is variable, though the disease course is generally considered mild. Available data could be influenced by cluster testing that occurs when a symptomatic parent tests positive for COVID-19. It is possible that when children are tested, they are still within the presymptomatic period of disease course [72]. A meta-analysis (n = 774) showed nearly all children who tested positive for COVID-19 only developed mild disease manifestation. An entirely asymptomatic course was reported in 19% of cases as compared to the 1% demonstrated in the adult population [42,63]. Severe disease was reported in only 3% of cases. The symptom prevalence is like that of the adult population, with fever and cough being the most reported symptoms. Still, they are reported to a lesser degree, with only half of the patients reporting fever or cough. Of note, while this analysis only demonstrated severe cases in 3% of patients, 43% reported the presence of G.I. symptoms [63].

Multisystem inflammatory syndrome in children (MIS-C)

In late April, clusters of children and adolescents started requiring admission to intensive care units at a rate disproportionately higher than COVID-19 trends thus far. Presenting symptoms included features that were similar to Kawasaki's disease and toxic shock syndrome [73]. Kawasaki's disease usually presents in children <5 years old, with less than 5% of cases presenting with cardiovascular shock requiring pressor management. Patients who present with Kawasaki disease-like features are of a median age of 8.3, and nearly half of patients ultimately receive vasopressor support [74]. MIS-C is proposed to be linked with SARS-CoV-2 infection, with 70% of patients testing positive for infection and 30% of patients demonstrating an epidemiological link to an infected person [74]. ACE2 expression is hypothesized to lower the risk of COVID-19 infection in children and account for the age-specific incidence of MIS-C [74,75].

Presentation in pregnant persons

The typical symptomatic presentation of fever and cough occurs significantly less often in pregnant patients than nonpregnant patients. Fever and cough were shown to have an incidence of 91% and 67% in the nonpregnant population as compared to only 51% and 31% in pregnant persons, respectively [76]. A diminished symptomatic presentation in pregnant patients warrants increased screening measures among this population due to demonstrated rates of increased preterm labor in COVID-19-positive pregnant patients [76]. Furthermore, when pregnant women presented symptomatically, 16.2% were admitted to an ICU and 8.5% required mechanical ventilation, with asymptomatic pregnant women who demonstrated none of these adverse outcomes [77].

Diagnosis and treatment

Overview

The WHO recommends that the decision for COVID-19 testing is based on clinical and epidemiological factors and should be linked to assessing the likelihood of infection [78]. Epidemiological factors include anyone who has had close contact with a patient with laboratory-confirmed COVID-19 within 14 days of symptom onset or a history of travel from affected geographic areas within 14 days of symptom onset [79]. To guide contact tracing, treatment options, and isolation requirements, the U.S.

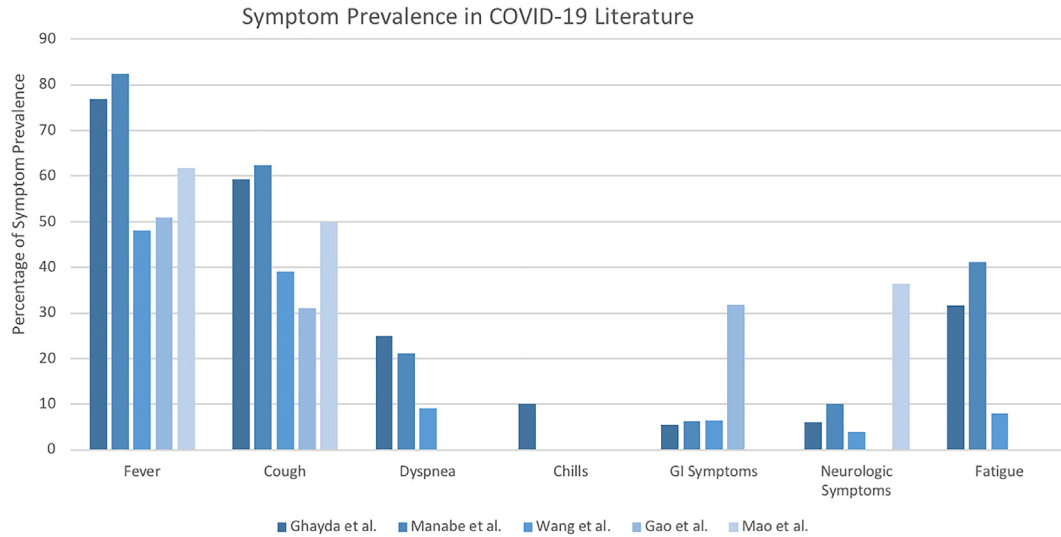


Fig. 1. Symptom prevalence in COVID-19 literature showing the presentation of fever, cough, dyspnea, chills, gastrointestinal symptoms, neurologic symptoms, and fatigue in recent literature.

CDC recommends using viral tests to diagnose acute infections in both symptomatic and asymptomatic individuals [80]. Virological testing should also be performed in people who are at a high risk of repeated exposure, such as healthcare workers and first responders [81]. Healthcare workers have a higher risk of reporting positive COVID-19 tests than the general community, and this risk increases in frontline workers without adequate access to PPE [82]. As these workers are treating COVID-positive patients, their health and wellness is crucial to the successful treatment of the COVID-19 pandemic [83]. Criteria for testing symptomatic patients include the presentation of clinical manifestations, recent visits to COVID prone countries, exposure to COVID-19 patients, and to detect the resolution of the disease. Criteria for testing asymptomatic patients include a known recent exposure to COVID-19 patients, unknown exposure to COVID-19 patients, olfactory dysfunction, the loss of smell and/or taste, transplant donors, and recipients [84]. Testing for all other pathogens and upper respiratory disease sources should also be performed during the initial evaluation, but should not delay the testing for SARS-CoV-2 [79,85]. Comorbid infections with other respiratory infections (viral, bacterial, and fungal) have occurred in COVID-19 patients. As a result, a positive test for a non-COVID-19 pathogen does not rule out SARS-CoV-2 or vice versa. Therefore, patients who meet suspected case definitions for COVID-19 should be tested whether or not another respiratory pathogen is found [41,78]. Other supplemental testing includes radiographic imaging such as serology testing, hematological testing, and chest CT scanning [84].

Nucleic acid amplification testing (NAAT)

Viral testing detects the SARS-CoV-2 nucleic acid or antigen [80]. Presently, suspected patients with COVID-19 are confirmed with viral RNA detection by nucleic acid amplification tests (NAAT) [78,84]. PCR is the gold standard test for the molecular diagnosis of viral or bacterial infections due to its high specificity and sensitivity [84]. NAAT methods, including reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification [86]. Although a diagnosis is made by the detection of SARS-CoV-2 through RT-PCR testing, a false-negative result may occur in 20%–67% of patients. This error is dependent on the quality and timing of the testing, as PCR positivity will be seen during early symptoms [87]. Upper respiratory tract (URT) viral load peaks around symptom onset, and viral shedding begins approximately 2–3 days before the onset of symptoms [88]. Because of the rate of false-negative result rates, clinical, laboratory, and imaging findings are also used to make a presumptive diagnosis [88]. PCR analysis also requires a variety of equipment and educated analysts, which can be found largely at well-established laboratories [89].

Currently, rRT-PCR is used with confirmation by nucleic acid sequencing, when necessary [41]. Thus far, the targeted viral genes include N, E, S, and RdRP [78,87]. Different conditions have been set and must be met, which depends on whether or not a patient is being tested in an area with or without known COVID-19 virus circulation. In areas with no known COVID-19 virus circulation, one of the following conditions must be met:

- A positive NAAT result for at least two different targets on the COVID-19 genome – of which at least one target is preferably specific for COVID-19 virus using a validated assay OR
- One positive NAAT result for the presence of betacoronavirus and COVID-19 virus further identified by sequencing partial or whole genome of the virus as long as the sequence target is larger or different from the amplicon probed in the NAAT assay used.

Ambiguity in results calls for resampling the patient, and if necessary, sequencing of the virus from the original specimen or of an amplicon generated from an appropriate NAAT assay. The NAAT assay must be different from the original assay used to obtain a reliable test result. For areas where the COVID-19 virus has been widely circulating, a simpler algorithm is sufficient for COVID-19 virus confirmation with NAAT. Although the use of rRT-PCR with one discriminatory target is considered sufficient for laboratory confirmation, one or more negative results do not rule out the possibility of SARS-CoV-2 active infection. The following factors may contribute to a false-negative result of a SARS-CoV-2 infected patient:

- Poor quality of the specimen, including containing little to no patient material (as a control, might be considered a human target in the PCR testing to determine if there is a sufficient amount of human DNA).
- Specimens were collected late or very early in the infection.
- Specimens not handled and shipped properly (nonmaintenance of the cold chain).
- Technical reasons that are inherent in the test (i.e., virus mutation or PCR inhibition) [78,87].

The WHO recommends that initial diagnostic testing be performed by collecting specimens of the URT, specifically nasopharyngeal and oropharyngeal swabs or wash in ambulatory patients [78]. If clinical suspicion remains, and URT RT-PCR is negative, LRT specimens should be collected from expectorated sputum or endotracheal aspirate/bronchoalveolar lavage in ventilated patients. Single negative URT results do not exclude a COVID diagnosis, so additional URT and LRT samples are recommended [41,78,87].

Serology testing

The U.S. CDC states that serological testing should not be used to establish the presence or absence of SARS-CoV-2 infection or reinfection, and the FDA has not authorized antibody tests to diagnose SARS-CoV-2 yet [80,90]. In cases where NAAT assays are negative, and there is a strong epidemiological link to COVID-19 infection, paired serum samples (in the acute and convalescent phase) could support this diagnosis once validated serology tests become available. Therefore, serum samples can be stored for these purposes [78].

Hematological testing

A meta-analysis between 3377 severe and non-severe COVID-19 patients, a significantly increased white blood cell count, and decreased lymphocytes (lymphopenia) and platelet counts (thrombocytopenia) were found in severe and fatal cases as compared to nonsevere disease and survivors. Furthermore, interleukins 6 (IL-6) and 10 (IL-10) and serum ferritin were found to be strong discriminators for severe disease [91]. Additional hematological findings are listed in the chart below. A metanalysis and systematic review of 43 studies involving 3600 patients revealed the most common hematological abnormalities as elevated C-reactive protein (68.6%), lymphopenia (57.4%), and increased lactate dehydrogenase (51.6%) [92].

An additional systematic review of 19 studies, including 2874 patients mostly from China, reported that the 88% who were hospitalized reported typical ranges of hematological abnormalities. Most of the reported characteristics are nonspecific and are common in pneumonia; therefore, hematological tests provide additional information about the progression or severity of the disease, not diagnostic [84,88]. Severe abnormalities have been associated with more severe infection, and D-dimer and lymphopenia (to a lesser extent) seem to have the largest prognostic associations [88]. See Fig. 2.

Computed tomography (CT) imaging

CT imaging has been routinely performed on COVID-19 patients. Chest CT is strongly recommended in suspected COVID-19 cases for initial evaluation and follow-up due to the respiratory system being primarily affected [93]. Although imaging is not used as a primary diagnostic tool, abnormal findings have been found in infected patients and might be an important tool in monitoring disease progression. Characteristic CT imaging abnormalities of COVID-19-infected patients include diffuse, peripheral ground-glass opacities [88]. A systematic search was conducted on 5041 COVID-19-infected patients from the onset of COVID-19 outbreak to April 20, 2020. Standard CT imaging features of patients with COVID-19 pneumonia included bilateral lung infections (80%), ground-glass opacities (65%), consolidation (22%), crazy paving pattern (12%), air bronchogram signs (18%), and intralobular septal thickening (27%) [86,93]. Of the 20% of patients who presented with unilateral lung involvement, 62% of patients demonstrated right lung involvement, with 74% of cases involving the right lower lobe.

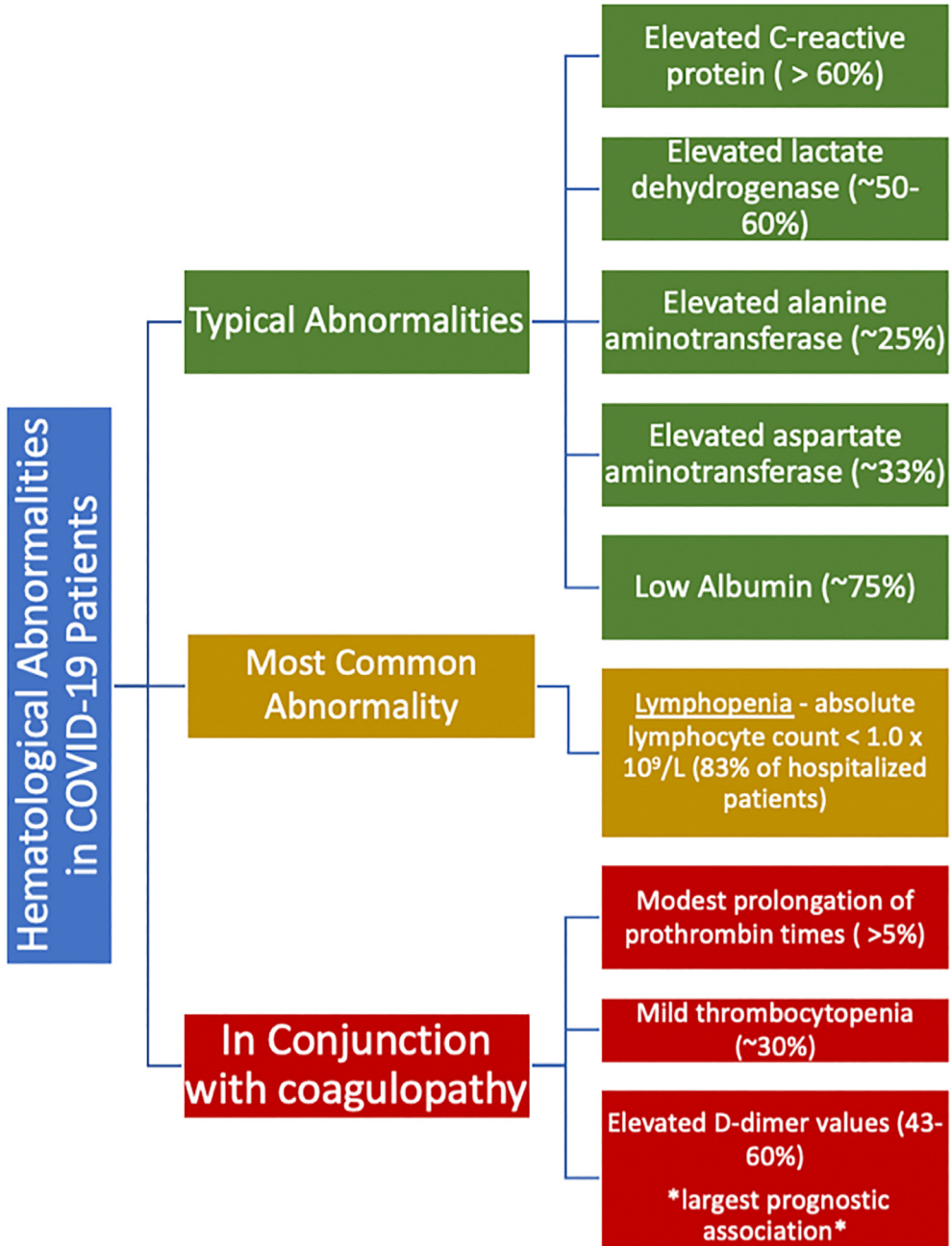


Fig. 2. Schematic of hematological abnormalities in COVID-19 patients.

Findings also showed that early disease revealed ground-glass opacities, followed by crazy paving development and increasing consolidation in the latter disease course [93]. CT abnormalities are nonspecific and can largely overlap with the presentation of other infections. Thus, the diagnostic value of CT imaging in SARS-CoV-2 patients is limited, as some confirmed cases show normal CT findings. In

contrast, other patients show abnormal CT findings consistent with COVID-19 days before detecting SARS-CoV-2 RNA in different patients [88]. Therefore, normal chest CT imaging findings cannot exclude COVID-19, even in symptomatic patients [94].

Treatment

Treatment varies depending on the severity of the disease, including mild, moderate, severe, and critical manifestations of COVID-19. The following sections outline the specific treatment management regimens for the differing clinical presentations of the SARS-CoV-19 virus. WHO has provided clinical management guidelines for each clinical manifestation, each of which is listed below in detail [41].

Mild COVID-19 patients (symptomatic treatment)

For patients with suspected or confirmed mild COVID-19, the first line of treatment is isolating the patient to contain viral transmission. This can be executed at a designated COVID-19 health facility, community facility, or at home (also known as self-isolation). The U.S. CDC recommends that for most persons with COVID-19, isolation and precautionary measures can generally be discontinued ten days after symptom onset and the resolution of fever for at least 24 h. These results were obtained without using fever-reducing medication, and other symptoms improved [90,95]. Decisions to isolate should be made on a case-by-case basis based on the local COVID-19 care pathway and should depend on clinical presentation, the requirement for supportive care, potential risk factors for severe disease, and conditions at home – particularly the presence of vulnerable persons in the household. Pharmacological remedies include symptomatic treatments such as antipyretics to assuage fever and pain and sufficient nutrition and rehydration. Additional counseling should be given to patients to educate them on the signs and symptoms of disease complications and progressions that require urgent care, particularly those with risk factors for severe illnesses. At-risk patients should be monitored closely, most notably for signs of rapid disease progression, including but not limited to lightheadedness, difficulty breathing, chest pain, and dehydration. Should patients develop life-threatening symptoms, they should immediately seek urgent care following the safety protocols established COVID-19 care pathways. Caregivers of children with mild COVID-19 must monitor for signs and symptoms of clinical deterioration, including but not limited to: difficulty breathing, fast or shallow breathing, blue lips or face, chest pain or pressure, new confusion, inability to awaken/not interacting when awake, inability to drink or keep down any liquids, and specifically for infants grunting or inability to breastfeed. Proper monitoring is accomplished through home-based, phone, telemedicine, or community outreach teams. Antibiotic therapy or prophylaxis for mild cases of COVID-19 are inadvisable, as they may lead to higher bacterial resistance rates that further propagate the burden of disease and deaths in a population during COVID-19 pandemic and beyond.

Moderate COVID-19 patients (pneumonia treatment)

Suspected or confirmed moderate COVID-19 cases, defined by the acquisition of pneumonia, should be isolated immediately to contain viral transmission. These patients may or may not require emergency interventions, however, they must be isolated regardless of suspicion or confirmed cases. The isolation protocol is found upon the established COVID-19 care pathways and is accomplished at a health facility, community facility, or at home. This decision should be made on a case-by-case basis and relies on clinical presentation, the requirement for potential supportive care and potentially vulnerable persons present in the household. Patients at high risk for deterioration should instead isolate at a hospital instead of isolation at home or community facilities. As with mild cases, febrile moderate COVID-19 cases should be tested and treated for other endemic infections that cause fever (i.e., malaria, dengue, etc.) per routine protocol if necessary, irrespective of the presence of respiratory signs and symptoms due to the possibility of coinfection. Patients with suspected or confirmed moderate COVID-19 should not be administered antibiotics unless under the clinical suspicion of bacterial infection. However, a recent systematic review reported only 8% of patients hospitalized with COVID-19-experienced secondary bacterial infection/fungal coinfection during hospital admission. For

older patients, particularly those in long-term care facilities, and children less than five years of age, providing empiric antibiotic treatment for possible pneumonia should be considered. Given these patients are not hospitalized, access to antibiotic treatment (e.g., co-amoxicillin) is sufficient, and the preferential treatment is broad-spectrum antibiotics. Hospitalized patients should be regularly monitored for vital signs using pulse oximetry while utilizing medical early warning scores (i.e., NEWS2 and PEWS) that facilitate the early recognition and escalation of treatment for deteriorating patients. At-home patients and caregivers should receive counseling on signs and symptoms of complications (i.e., difficulty breathing, chest pain, etc.), informed to seek urgent care immediately if such complications arise [41].

Severe COVID-19 patients (severe pneumonia treatment)

The immediate administration of supplemental oxygen is paramount to any of the patients exhibiting emergency signs or to patients with a reading of $\text{SpO}_2 < 90\%$. The most frequent emergency signs are as follows: obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, convulsions, and/or coma. Device selection for the delivery of appropriate flow rates include nasal cannula for flow rates up to 5 L/min; Venturi mask for 6–10 L/min; and face mask with reservoir bag for 10–15 L/min. Adult patients with said emergency signs must receive emergency airway management and target oxygen levels of $\text{SpO}_2 \geq 94\%$. When patients have stabilized, oxygen target levels aim for $\text{SpO}_2 > 90\%$ in nonpregnant adults and $\text{SpO}_2 \geq 92\%$ – 95% in pregnant women. After resuscitation and stabilization of pregnant patients, fetal well-being should be monitored, with frequency of fetal heart rate observed as a function of gestational age, maternal clinical status (e.g., hypoxia), and fetal conditions. Children with emergency signs should also target oxygen levels of $\text{SpO}_2 \geq 94\%$ during resuscitation and $\text{SpO}_2 > 90\%$ when stable; however, they should receive oxygen through nasal cannula or prongs if the patient is a particularly young child due to better tolerance of the procedure. Adults can also employ techniques such as positioning. For example, a high supported sitting posture potentially assists in optimizing oxygenation, easing breathlessness, and reducing energy expenditures. Spontaneously breathing patients may also improve oxygenation and their ventilation/perfusion ratio while in prone position when awake, but there lacks evidence to support this technique; therefore, this should be done under a clinical trial protocol to assess efficacy and safety before implementation. For adult patients who present with increased secretion production, secretion retention, and/or weak cough, airway clearance management may assist with proper secretory mechanisms and includes gravity-assisted drainage with activated cycles of breathing techniques. Mechanical insufflation-exsufflation and inspiratory positive pressure breathing should be avoided when possible, and the implementation of the aforementioned techniques must be personalized for each respective patient.

Patients should be monitored for signs of clinical deterioration (rapidly progressive respiratory failure and shock) and be immediately given supportive care interventions when circumstances dictate. Hematological and biochemical laboratory testing, ECG, and chest imaging should be performed at admission and as clinically indicated to monitor for complications. These complications include acute respiratory distress syndrome, acute liver injury, acute kidney injury, acute cardiac injury, DIC and/or shock. The application of timely, effective, and safe supportive therapies provides the cornerstone of therapy for patients who develop severe manifestations of COVID-19. Signs and symptoms suggestive of venous or arterial thromboembolism should be monitored closely – which considers the possibility of stroke, DVT, pulmonary embolism, or acute coronary syndrome. Any of these manifestations when presented would elicit the corresponding course of action in accordance with hospital protocols for these diagnoses. Fluid management in adults and children, particularly intravenous fluids, should be treated with caution in patients without tissue hypoperfusion and adequate fluid responsiveness as aggressive fluid resuscitation may worsen oxygenation in situations involving limited availability of mechanical ventilation [41].

According to the U.S. CDC, a limited number of individuals with severe illnesses may produce a replication-competent virus beyond 10 days of onset (typical isolation protocol), which may warrant the extension of the duration of isolation and precautionary measures for up to 20 days after symptom onset. With this in mind, consultation with infection control experts would be beneficial [90].

*Critical COVID-19 patients (ARDS – acute respiratory distress syndrome)**Management of adult and pediatric patients with mild ARDS who are treated with noninvasive or high-flow nasal oxygen (HFNO) systems*

Patients with COVID-19 who have mild ARDS, a trial of HFNO, noninvasive ventilation are able to use continuous positive airway pressure (CPAP) and bilevel positive airway pressure. Although HFNO may reduce the need for intubation as compared to standard oxygen therapy, patients with hypercapnia, hypoxemic respiratory failure, and hemodynamic instability, multiorgan failure, or abnormal mental status, should not receive HFNO in place of options such as invasive ventilation. NIV guidelines make no recommendations for their applicability in hypoxemic respiratory failure (apart from cardiogenic pulmonary edema, postoperative respiratory failure, and early NIV for immunocompromised patients) or in pandemic viral illness (referring to studies from SARS and pandemic influenza). Risks can include delayed intubation, large tidal volumes, and injurious transpulmonary pressure, and the limited data available suggest a high failure rate with other confounding viral infections such as MERS-CoV receiving NIV. Patients receiving a trial of HFNO or NIV should be monitored by personnel experienced in performing endotracheal intubation in case the patient acutely deteriorates or does not improve after the short trial (about 1 h), to ensure immediate intubation should these conditions present themselves. HFNO systems can deliver 60 L/min and up to 1.0 fraction of inspired oxygen (FiO₂) in adults, whereas pediatric circuits can handle up to 25 L/min. Pediatric patients may still require adult circuits to deliver adequate flow. Situations where mechanical ventilation may not be available warrants the administration of bubble nasal CPAP for newborns and children with severe hypoxemia. Because of uncertainty about *aerosolization*, airborne precautions should be accounted for with HFNO, NIV, and bubble CPAP [41].

Recommendations for adult and pediatric patients with ARDS who need intubation and IMV

Patients may continue to have increased labored breathing or hypoxemia even with oxygen delivery through a face mask with a reservoir bag (flow rates 10–15 L/min i.e., minimum flow required to keep bag inflation, FiO₂ 0.60–0.95). Hypoxemic respiratory failure in ARDS commonly results from an intrapulmonary ventilation-perfusion mismatch or shunt and requires mechanical ventilation. Researchers recommend promptly recognizing progressive acute hypoxemic respiratory failure when a patient is in respiratory distress and adequately preparing to provide advanced oxygen/ventilation support when necessary. Endotracheal intubation is recommended using airborne precautions, with rapid-sequence intubation being appropriate after an airway assessment that identifies no signs of difficult intubation. Patients with ARDS, particularly young children, obese, or pregnant patients, may desaturate quickly during intubation; therefore, it is recommended to preoxygenate with 100% FiO₂ for 5 min using a face mask with reservoir bag. When possible, avoid bag-valve mask ventilation to reduce exposure to aerosols [41].

Recommendations pertaining to mechanically ventilated adult and pediatric patients with ARDS

Implementation of mechanical ventilation using lower tidal volumes (4–8 mL/kg predicated body weight [PBW]) and lower inspiratory pressures (plateau pressure < 30 cmH₂O) is strongly recommended for adults and is also suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria. Initial target tidal volume is 6 mL/kg PBW; tidal volume up to 8 mL/kg PBW is allowed if undesirable effects occur such as desynchrony or pH < 7.15. Permissive hypercapnia is permitted and use of deep sedation may be required to control respiratory drive and achieve tidal volume targets. Children have a lower targeted level of plateau pressure (<28 cmH₂O), and a lower target of pH levels is permitted (7.15–7.30). Tidal volumes should be adapted to disease severity: 3–6 mL/kg PBW in the case of poor respiratory system compliance and 5–8 mL/kg PBW with a better conserved compliance.

Adult patients with severe ARDS (partial pressure of arterial oxygen: PaO₂/FiO₂ < 150) are recommended to receive prone ventilation for 12–16 h per day. Pediatric patients with severe ARDS can also be considered, but this treatment requires sufficient human resources and expertise to be safely performed. There is little evidence supporting this method for pregnant women with ARDS, although it could be considered in early pregnancy. Pregnant women in their third trimester may benefit from

being placed in the lateral decubitus position. Physicians should implement conservative fluid management for ARDS patients without tissue hypoperfusion and fluid responsiveness to shorten the duration of ventilation.

In patients with moderate or severe ARDS, trials of higher-end positive-end-expiratory pressure (PEEP) are recommended over those of lower PEEP. However, they require a risk-benefit analysis—corresponding to risks of end-inspiratory distention and higher pulmonary vascular resistance versus the benefit of reducing atelectrauma and improving alveolar recruitment. It is suggested to individualize the PEEP where during titration the patient is monitored for beneficial or harmful effects and driving pressure. In younger children, maximal PEEP pressures are 15 cmHO. When disconnection is required (e.g., transfer to a transport ventilator), use in-line catheters for airway suctioning and clamp the endotracheal tube, concurrently utilizing ventilator hyperinflation as opposed to manual hyperinflation. For patients with excessive secretions or difficulty clearing secretion, consider the application of airway clearance techniques if deemed medically appropriate [41].

Recommendations pertaining to adult and pediatric patients with ARDS in whom lung protective ventilation strategy fails to achieve adequate oxygenation and ventilation

Patients who have refractory hypoxemia (i.e., including a ratio of PaO2 to the FiO2 of <50 mmHg for 3 h, a PaO2: FiO2 of <80 mmHg for > 6 h) despite having lung protective ventilation, should be referred to the treatment of COVID-19. Although ECMO was not statistically significant in primary outcomes of 60-day mortality between ECMO and standard medical management, it was associated with a reduced risk of mortality and crossover to ECMO treatment. A post-hoc Bayesian analysis of this RCT showed that ECMO has a notable probability to reduce mortality across a range of prior assumptions. In patients with MERS, ECMO vs. conventional treatment was associated with reduced mortality in a cohort study but is deemed a resource-intensive therapy that necessitates expert centers. Children with severe ARDS can be put on ECMO, but there is not much evidence supporting its therapeutic effects in this population [41].

Remdesivir

On October 22, 2020, the FDA approved the antiviral drug, remdesivir, to treat COVID-19 [17,18]. Remdesivir is for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kg (88 pounds) for the treatment of COVID-19 that requires hospitalization. Remdesivir can be administered in a hospital or treatment facility capable of delivering acute care equivalent to inpatient hospital care. Remdesivir is the first medication for COVID-19 to be approved by the FDA. See Table 1.

The FDA originally issued an Emergency Use Authorization (EUA) on May 1, 2020 for the use of remdesivir for the treatment of hospitalized adult and pediatric patients with severe COVID-19 (low blood oxygen levels or needing oxygen therapy or more intensive breathing support). The EUA was reissued on August 28, 2020 to expand the treatment of all hospitalized adult and pediatric patients with suspected or laboratory-confirmed COVID-19, irrespective of their severity of disease [96]. As of

Table 1
Side effects associated with antivirals, immunomodulators, or plasma therapy.

Agent	Class	Side Effects
Chloroquine and hydroxychloroquine ± azithromycin	Antimalarial	QT prolongation and taken together increases risk of cardiotoxicity.
Lopinavir/ritonavir	Antiviral	Most commonly adverse are GI.
Remdesivir	Antiviral	Elevation of hepatic enzymes, GI complications, rash, renal impairment, and hypotension.
Umifenovir	Antiviral	Diarrhea and nausea.
Favipiravir	Antiviral	QT interval prolongation.
Interferon-β-1a	Immunomodulator	Pyrexia and rhabdomyolysis.
Tocilizumab	Immunomodulator	URT infections, nasopharyngitis, headache, hypertension, increased alanine aminotransferase (ALT) and injection site reactions.

October 22, 2020, remdesivir is the first treatment for COVID-19 to receive FDA approval [97]. It is indicated for the treatment of hospitalized cases of COVID-19 in adults and children 12 years or older and weighing at least 40 kg. It should only be administered in a hospital or healthcare setting capable of providing acute care comparable to hospital care. The FDA also revised the EUA for remdesivir to authorize the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients (3.5 kg to less than 40 kg) or hospitalized pediatric patients (less than 12 years old and weighing at least 3.5 kg). Clinical trials that assess the safety and efficacy in this pediatric population continue today.

Approval of a new drug product under the Federal Food, Drug, and Cosmetic Act requires substantial evidence of effectiveness and a demonstration of safety for the drug's intended use(s), passing a rigorous scientific benefit-risk assessment to ensure that benefits outweigh its risks of intended population. See Table 2 [15,98,99].

Remdesivir is an antiviral agent (a SARS-CoV-2 nucleotide analogue RNA polymerase inhibitor) that was initially designed to combat the Ebola virus disease [100,101].

Contraindications include hypersensitivity reactions to remdesivir or any components of the product, and lower infusions rates can be considered to potentially prevent signs and symptoms of hypersensitivity, but treatment should be discontinued should signs and symptoms of clinically significant hypersensitivity reaction persist. Before initiation and during treatment all patients should have renal and hepatic laboratory testing performed and prothrombin time assessed as clinically appropriate. The most common adverse reactions observed (calculated as incidence rates greater than or equal to 5%, all grades) include nausea, ALT increased, and AST increase. Increased risk of

Table 2

Data from three randomized controlled clinical trials involving Veklury (remdesivir), including patients hospitalized with mild-to-severe COVID-19. ** indicates statistically significant results.

<p>Study: A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults (ACTT-1)</p> <ul style="list-style-type: none"> • Randomized, double-blind, placebo controlled clinical trial. • Conducted by National Institute of Allergy and Infectious Diseases. • Measure: How long it took for subjects to recover from COVID-19 within 29 days of being treated. • Patient population: mild, moderate, and severe COVID-19 (n = 1062). • Treatment: Veklury (n = 541) or placebo (n = 521), plus standard of care. • Recovery defined as either a) being discharged from the hospital or b) being hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care. • Results: median recovery time 10 days for Veklury; 15 days for placebo. **statistically significant • Odds of clinical improvement at Day 15 statistically significantly higher in the Veklury group when compared with the placebo group.**
<p>Study: Evaluation of the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Moderate Coronavirus Disease (COVID-19) as Compared to Standard of Care Treatment</p> <ul style="list-style-type: none"> • Randomized, open-label, multicenter clinical trial. • Measure: Evaluation of the clinical status of subjects on day 11. • Patient population: Hospitalized adult subjects with moderate COVID-19 (n = 584). • Treatment: Veklury for 5 days (n = 191), Veklury for 10 days (n = 193), and standard of care (n = 200). • Results: • Overall, the odds of a subject's COVID-19 symptoms improving were statistically significantly higher in the five-day Veklury group at day 11 than those only receiving standard of care.** • The odds of improvement with the 10-day treatment group when compared with those receiving only standard of care were numerically favorable, but not statistically significantly different.
<p>Study: A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19</p> <ul style="list-style-type: none"> • Randomized, open-label, multicenter clinical trial. • Measure: Evaluation of clinical status of subjects on day 14. • Patient population: Hospitalized adult subjects with severe COVID-19 (n = 397). • Treatment: Veklury for 5 days (n = 200) and Veklury for 10 days (n = 197). • Results: Odds of subject's COVID-19 symptoms improving were similar for those in the five-day Veklury group as those in the 10-day Veklury group; no statistically significant differences found in recovery rates or mortality rates between the two groups.

transaminase elevation has been reported in both healthy volunteers and patients with COVID-19 who have received remdesivir treatment [101].

The further development of future treatments for COVID-19 could use nanotechnology to address limitations of antiviral therapy. Nano-intervention is aimed at designing effective nanocarriers to counter the conventional limitations of antiviral and biological therapeutics. SARS-CoV-2 targets human cells through the characteristic viral structural spike protein (S- spike glycoprotein) that binds to ACE2 receptor [102]. The Interaction between viral S protein and ACE2 on the host cell surface is of significant interest because it initiates the infection process. Engineered nanocarriers would allow the blocking of the initial interactions of viral spike glycoproteins with host cell surface receptors; therefore, disrupting virion construction [103]. They can also be utilized in designing risk-free and effective immunization strategies for SARS-CoV-2 vaccine candidates such as protein constructs and nucleic acids.

Influenza and COVID-19: present challenge of 2020–2021 flu season

The treatment of influenza is similar in all patients, regardless of SARS-CoV-2 coinfection. The NIH reports that the Panel recommends hospitalized patients be started on empiric treatment for influenza with oseltamivir (antiviral treatment) as soon as possible, regardless if influenza testing results have been received. If URT NAAT rules out influenza for nonintubated patients and both URT and LRT specimens for intubated patients, oseltamivir can be stopped. The clinical presentation of an uncomplicated, clinically mild influenza case can overlap with mild COVID-19 presentation. While ageusia and anosmia can occur with both diseases, they are more common with COVID-19 than influenza. Fever is also not always present in patients with either disease, in particular, the elderly or immunocompromised patients. Although complications of both diseases can be similar, the onset of influenza complications and severe disease usually occurs within a week of illness onset, as opposed to severe COVID-19 that occurs in the second week of illness. This overlap in signs and symptoms requires diagnostic testing for both viruses while they are cocirculating to distinguish between the two, or to identify coinfection that has been reported with both influenza A and B viruses with SARS-CoV-2 [104,105]. At this time, there is no information on the frequency, severity, and risk factors for coinfection with these viruses versus either alone [106].

Recent clinical studies

Many vaccine candidates, such as mRNA-1273, are now in phase III clinical trials and vaccinations have now begun with the recent FDA approval of the vaccines produced by Pfizer and Moderna. However, it is unlikely that a vaccine against the virus will be available to the general public before the end of 2020, since it is currently being administered to frontline healthcare workers and residents of long-term care facilities [107]. As such, a considerable amount of research has focused on repurposing existing antivirals and immunomodulators for the treatment of this novel virus [108].

Antiviral treatment: viral protease inhibitors

Viral protease inhibitors work to hinder viral replication by interfering with the processing of viral polypeptides. Most clinical trials have concentrated on viral protease inhibitors lopinavir/ritonavir, as these have shown to be effective treatments *in-vivo* and *in-vitro* for the previous coronavirus outbreaks, MERS-CoV and SARS-CoV [108,109]. Despite this, lopinavir/ritonavir treatment in a randomized trial involving 199 patients with severe cases of COVID-19 showed no additional benefit to patients as compared to standard care treatment [110]. Additionally, in a randomized phase II trial involving 127 patients with mild to moderate COVID-19, treatment with lopinavir/ritonavir had effects comparable to placebo [111]. Notably, both trials reported numerous limitations, so further research on lopinavir/ritonavir's effectiveness is necessary.

Antiviral treatment: RNA polymerase inhibitors

RNA polymerase inhibitors, namely remdesivir and favipiravir, disrupt the replication of the viral genome and therefore, may be promising treatments for COVID-19 [108,112]. In a randomized, double-

blind clinical trial, preliminary results found that IV remdesivir given over ten days significantly reduced time to recovery. Additionally, mortality decreased in those given IV remdesivir as compared to placebo, though this difference was not significant [17]. Favipiravir may also be an effective treatment as it resulted in faster viral clearance and improved chest imaging as compared to patients taking lopinavir/ritonavir in a nonrandomized trial [113].

Antiviral treatment: fusion inhibitor

Hydroxyquinoline, an immunosuppressive and anti-malarial drug that blocks viral fusion, has shown to inhibit SARS-CoV-2 *in-vitro* [114]. However, results from clinical trials evaluating its clinical effectiveness in COVID-19 patients are mixed. An open-label non-randomized trial with 36 positive COVID-19 patients found hydroxyquinoline and azithromycin significantly reduced viral load [115]. Conversely, in a more recent double-blind, randomized trial, hydroxyquinoline did not prevent infection when used as postexposure prophylaxis [116]. There are currently ongoing clinical trials to elucidate hydroxyquinoline's effectiveness against COVID-19 [117–119].

Immunomodulators

Type I IFN-I are crucial for protection against viral infections, and it has been suggested that SARS-CoV-2 can evade or inhibit their production [120]. In a randomized clinical trial consisting of 81 participants, subcutaneous administration of IFN β -1a to COVID-19 patients significantly reduced 28-day mortality as compared to the control group, particularly if given early after the onset of symptoms. Additionally, while IFN β -1a administration did not affect clinical response time, the discharge rate was significantly increased by day 14 [121]. Furthermore, the combination therapy involving IFN β -1b, ribavirin, and lopinavir/ritonavir resulted in significantly reduced viral shedding [111]. Another immunomodulator worth mentioning is tocilizumab, a monoclonal antibody that attenuates IL-6, a proinflammatory cytokine that may contribute to the fatality of COVID-19 patients [122]. Preliminary reports of an open-label randomized control trial involving 129 patients with moderate to severe COVID-19 related pneumonia have reported significantly reduced mortality or need for ventilation as compared to the control group. Note that this trial is pending peer review, and further research is warranted [123].

Summary

With over one million confirmed deaths to date, COVID-19 is the deadliest pandemic of the twenty-first century, matched only in recent history by the influenza pandemics of 1918, 1957–1958, and 1968–1970 and the ongoing HIV/AIDS pandemic [10,124–127]. This outbreak will have lasting, widespread socioeconomic effects, including disruption to education, business, and healthcare globally [128]. The need for effective diagnosis and treatment methodologies, grounded in understanding this virus's microbiology and pathophysiology, is clear.

In summary, coronaviruses are a family of enveloped RNA viruses characterized by a large genome and characteristic glycoprotein spikes. Replication of the coronavirus genome is aided by proofreading machinery, unique to coronaviruses, and necessary to maintain their relatively large genome. The process of translation in coronaviruses is unique due to the presence of ribosome frameshifting [1,2,129]. Coronaviruses utilize surface glycoproteins to bind to and enter host cells; in SARS-CoV-2, the novel coronavirus responsible for COVID-19, this glycoprotein binds host ACE2 receptors. Coronavirus infection in humans is typically mild and self-limited, confined to the upper respiratory tract, but novel strains of coronavirus can cause severe disease affecting the lungs and other organ systems. Elderly patients and those with comorbidities are particularly susceptible [9].

COVID-19 presents with fever, lethargy, and dry cough and may progress to pneumonia, respiratory failure, multisystem organ dysfunction, and death [11–13,21]. Treatment is primarily supportive, with escalation from supplemental oxygen to noninvasive positive pressure ventilation or mechanical ventilation appropriate for respiratory impairment [21]. Corticosteroids have also proven useful as an adjunctive treatment [22,23]. Some effective antiviral agents have been identified and are being used in

particular clinical scenarios, while the search for additional treatments for this history-defining disease continues [21,130]. The development of a vaccine has progressed significantly; it has now been approved by the FDA on an emergency basis and is expected to be administered to the general population in the coming months.

Practice Points:

- Coronavirus infection in humans is typically mild and self-limited, confined to the upper respiratory tract, but novel strains of coronavirus can cause severe disease that affects the lungs and other organ systems.
- COVID-19 presents with fever, lethargy, and dry cough and may progress to pneumonia, respiratory failure, multisystem organ dysfunction, and death.
- Treatment is primarily supportive, with escalation from supplemental oxygen to noninvasive positive pressure ventilation or mechanical ventilation appropriate for respiratory impairment.
- Corticosteroids have also proven useful as an adjunctive treatment.
- Several vaccines have been developed and some were recently approved by the FDA; they should be available to the general public by 2021.

Research Agenda:

- Most effective preventative strategies to decrease the spread of COVID-19.
- Antiviral agents that can treat existing COVID-19 infection effectively, with no significant side effects.
- Rapid testing techniques that can be made widely available to clinicians and consumers.
- COVID-19 vaccine development that is safe and effective.

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Declaration of competing interest

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