

PRIMARY CARE REPORTS

The Practical CME Journal for Primary Care and Family Physicians

May 2020

VOL. 26, NO. 5

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**The information presented in
this article is based on the latest
available data at press time.
This article will discuss off-label
use of medication not approved
by the U.S. Food and Drug
Administration.**

STATEMENT OF FINANCIAL DISCLOSURE

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COVID-19: What Providers Should Know

Introduction

The disease associated with the 2019 novel coronavirus (COVID-19) is now a significant event in world history, with uncertain but likely major consequences for individuals, families, healthcare workers, health systems, and the global economy. There still is a great deal to be learned. Although COVID-19 appears to pose only a limited danger to children, older adults face the possibility of much more serious manifestations. In addition, healthcare professionals and systems are under serious threat of being overwhelmed. Staff may be in shortage because of illness or the need for isolation. Hospital systems may need to divert resources from areas and specialties under less strain than others. In short, at this time it seems COVID-19 will demand the attention of most practitioners and allied health providers over the next year. Thus, familiarity with what is known so far about its pathophysiology, epidemiologic risk factors, treatment, and future directions for research is important as we face and fight this crisis united as healthcare providers.

Terminology

During crisis situations, accurate communication is vital to ensure healthcare providers and the public are properly informed. Thus, consistent terminology should be used when discussing COVID-19. Because of the novel character of this virus and to ensure the proper epidemiologic terms are employed, the following definitions may be helpful:

Severe acute respiratory syndrome (SARS): The infectious disease caused by a zoonotic coronavirus (SARS-CoV) that spread between multiple countries in East Asia and Canada in 2002-2003.¹

Middle East respiratory syndrome (MERS): The infectious disease caused by a zoonotic coronavirus (MERS-CoV) that spread between multiple countries in the Middle East and South Korea from 2012 to the present.²

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): The currently proposed name of the virus related to the December 2019 outbreak in Wuhan, China.¹ The name is proposed by the Coronavirus Study Group of the International Committee on the Taxonomy of Viruses. In materials distributed for the public, the World Health Organization (WHO) also will refer to the virus as "COVID-19 virus" to avoid confusion.³

Coronavirus Disease 2019 (COVID-19): The currently accepted name by WHO for the disease caused by SARS-CoV-2.³ The name was chosen

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IMPLICATIONS OF COVID-19 FOR PRIMARY CARE

By Gregory R. Wise, MD, FACP, Editor in Chief

In a recent survey of 500 primary care physicians (PCPs), nearly half had no capacity to test patients for COVID-19, more than one-fifth reported a severe impact on their practice, and another 30% reported the strain as “close to severe.” Many practices had been affected by being overwhelmed by patients’ virtual questions, a lack of supplies, and clinicians out of work because of illness or self-quarantine.¹

Diagnosis

PCPs often are the first to communicate with potential COVID-19 patients. Without definitive testing, it is challenging to reliably be able to provide an accurate differential diagnosis, but there is a developing list of signs and symptoms associated with COVID-19. Unfortunately, this list is quite broad, nonspecific, and variable. The most common symptoms have been fever, cough, fatigue, sputum production, shortness of breath, sore throat, and headache.^{2,3} Other presentations include anosmia and dysgeusia, as well as gastrointestinal symptoms, such as abdominal pain and diarrhea.⁴

Typically, shortness of breath, chest pressure, and hypoxia come on later, but sometimes can develop quite rapidly, resulting in the need for urgent hospitalization and ventilator support. Early in the pandemic, PCPs did not have ready access to testing for their patients. Now, increasing access, with more rapid turnaround times, helps with the accurate identification of patients and the promotion of effective self-quarantining. The PCP should be familiar with the local testing sites for referral and needs to provide an order in harmony with currently evolving guidelines.

Prognosis

It is well recognized now that the risk of serious morbidity and mortality is linked to underlying conditions, such as advanced age, hypertension, diabetes, kidney disease, smoking, cardiovascular disease, lung disease, and cancer.⁵ Death rates are difficult to calculate accurately as a result of inadequate testing, but reports have ranged from 1% to 12%.⁶ It is also becoming clear that men and African-Americans are disproportionately showing higher mortality rates.⁷

Treatment

Although there currently is no approved treatment for COVID-19, four areas of research show promise: antivirals, convalescent sera, monoclonal antibodies, and vaccine. Antivirals now being studied include the RNA polymerase inhibitor remdesivir, lopinavir/ritonavir, favipiravir, hydroxychloroquine, and chloroquine.⁸

Unfortunately, a recent study employing lopinavir-ritonavir did not significantly advance clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with serious COVID-19.⁹

An encouraging Australian study of the Food and Drug Administration-approved antiparasitic drug ivermectin has shown it to have broad-spectrum antiviral activity in vitro, resulting in a

5,000-fold reduction of SARS-CoV-2 viral RNA at 48 hours.¹⁰

N-acetylcysteine has been investigated in improving cell immunity and attenuation of influenza, and investigational trials are underway to aid in treating acute respiratory distress syndrome.¹¹ Patients in the United States already have been treated with convalescent sera with encouraging results. Vaccine development is well underway but is not expected to be available in 2020.

Telemedicine

Telemedicine for PCPs has exploded because of the pandemic’s need for social distancing whenever possible. The Centers for Medicare & Medicaid Services has provided a Medicare fact sheet for coverage and payment, as have many other third-party payers.¹² This technology comes with advantages and shortcomings. Like a virtual house call, often for the first time the PCP can see the patients and household members in their homes and can observe living conditions and environments that could not be easily assessed with an office visit. With videoconferencing, the physician can maintain eye contact, whereas in the office there often has been the distracting challenge of looking at the patient while entering data into the electronic medical record. Be alert to the increased risk of domestic violence for partners who are sheltering in place. Address control of modifiable comorbid conditions, such as diabetes and hypertension. Reinforce the benefit of social distancing and basic principles of hygiene. Look for developing or worsening anxiety and depression. General nutritional and immune-boosting recommendations that are inexpensive and reasonably safe when used judiciously might include the use of vitamin C, zinc, selenium, and multivitamins.¹³

Although not a substitute for the established public health initiatives, patients often want to do something. The PCP’s role also should help screen questions from patients regarding the proliferating scams and internet “cures.” Encourage those who have recovered to donate plasma.

Advance Directives

PCPs always have been encouraged to be proactive in addressing end-of-life issues with patients, but this might be a particularly appropriate time to be aware of patients’ wishes and be sure they have discussed advance directives and durable power of attorney for healthcare decisions with their families. This need has been highlighted by heartbreaking stories of spouses separated at the emergency department because of strict visitation limitations and not being able to see or communicate with their loved one as he or she progresses through respiratory collapse, ventilator support, and death. The risk of mortality increases with the duration of ventilator use.

Mitigation Measures

Telemedicine is a good opportunity to reinforce the adherence to public health measures, such as social distancing, disinfection of surfaces, frequent handwashing with soap and water for 20 seconds, and the use of cloth masks when outside the home with

potential close contact with others. Social distancing is stressful, particularly for older patients who are unable to visit children and grandchildren. State and national guidelines will be reduced at some point, but that will not mean the risk of infection and its complications will plummet to zero, particularly for patients with underlying conditions, especially if the infection resurfaces in the fall.

Keeping Perspective

A widely circulating worst-case scenario by the Coronavirus Task Force projected up to 240,000 deaths in the United States by August, assuming perfect social distancing practices. There are 60 million Americans over the age of 65 years. Even if all the deaths occurred in this high-risk age group, that would be an overall fatality rate of “only” 0.4%. Alarming and tragic indeed, but not the bubonic plague. Fortunately, updated models are showing much lower death projections, presumably based on the effectiveness of mitigation measures.

Like every other pandemic, this one will end. America may look and behave very differently, but hopefully be better prepared for the next one. PCPs may be much more likely to be on the frontlines in that one.

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Continued from page 49

following international guidelines to avoid stigmatizing any particular location, region, animals, or food items.⁴

Endemic: A disease that is constantly present, prevalent, and expected in a given area.⁵

Epidemic: A sudden rise in the cases of a disease beyond what normally is expected.⁵

Outbreak: The same definition as epidemic, but generally in a more limited area (such as a city or province).⁵

Pandemic: An epidemic that has spread across multiple countries.⁵

Microbiology of Coronaviruses

Coronaviruses are named for the club-like projections of surface proteins from the virus particle that appear to create a crown, or “corona,” on electron

micrographs.⁶ (See Figures 1 and 2.)

Coronaviruses are enveloped, nonsegmented, single-stranded, positive-sense ribonucleic acid (RNA) viruses, with the largest known genome among all viruses (approximately 30 kb).^{6,7}

Numerous coronaviruses are known to cause diverse clinical syndromes in humans and animals, including mild to severe disease in such species as bats, rats, mice, chickens, turkeys, cattle, beluga whales, dogs, cats, rabbits, livestock, and pigs.⁷ In these animals, disease can manifest in the central nervous system, the respiratory tract, the gastrointestinal (GI) tract, the hepatobiliary system, and the renal system.⁷

Pathogenic human coronaviruses (HCoV)s were identified first in the 1960s.⁸ Four strains of community-transmitted, seasonal HCoV)s now have been identified: HCoV 229E, OC43,

NL63, and HKU1. Each of these coronaviruses is an endemic cause of generally mild, self-limited respiratory infections in children and adults. Notably, 60% to 90% of adults will become seropositive for at least one of these viruses in their lifetime.⁶

The novel coronaviruses SARS-CoV and MERS-CoV emerged in 2003 and 2012, respectively, causing major epidemics of severe respiratory illnesses. SARS-CoV was determined to have a natural reservoir in horseshoe bats, supported by findings of highly conserved SARS-related CoVs in bats that use the same cellular receptor as the human virus.⁹ There also were findings of similar viruses in palm civets and other mammals that were postulated to act as intermediate animal hosts in the “wet markets” (exotic animal and seafood markets) of China. MERS-CoV

also has been linked to previously identified bat coronaviruses, with the dromedary camel acting as an intermediate host.¹⁰ After containment of both of these outbreaks, it was suggested that new, zoonotic coronaviruses would continue to emerge in the future, causing novel human and animal diseases through their ability to recombine and infect multiple species and cell types.⁷

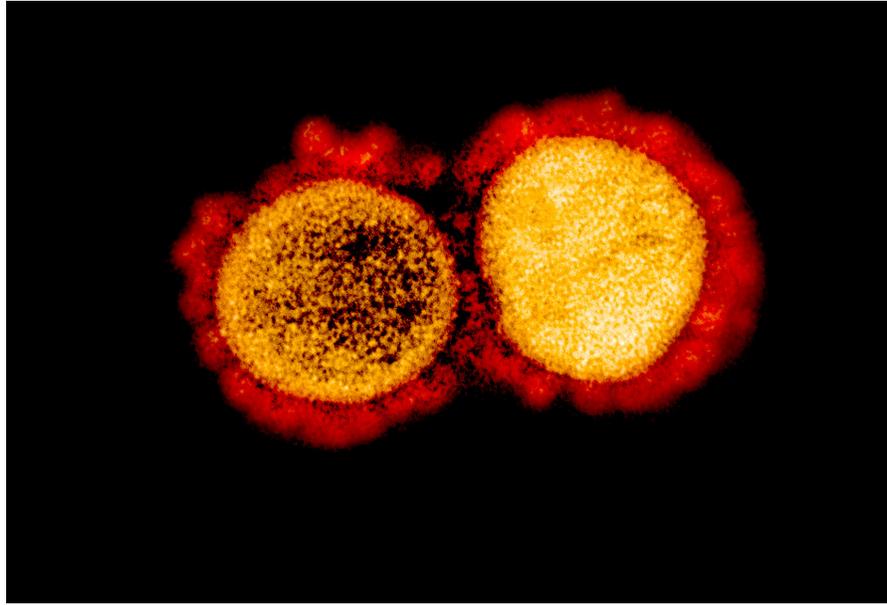
Novel 2019 Coronavirus

In December 2019, an outbreak of pneumonia of unknown etiology emerged in Wuhan, China, with a case cluster apparently linked to the Huanan Seafood Wholesale Market — a marketplace for seafood and various animals from regions throughout East and Southeast Asia.¹¹ These cases were identified using a reporting mechanism for “pneumonia of unknown etiology” that originally had been developed in the wake of the previous SARS epidemic.¹² Although retrospective case identification was able to pinpoint cases of pneumonia associated with the Huanan Seafood Wholesale Market as early as Dec. 13, 2019, further cases with no clear epidemiologic link were identified as early as Dec. 1, 2019.¹³ This suggested that transmission potentially had occurred as early as November 2019, but had been undetected.

The China Center for Disease Control and Prevention (China CDC) conducted initial viral studies, which included lower respiratory tract samples, in four of the known patients from the December 2019 cluster. In these patients, no specific pathogens could be identified by the RespiFinderSmart22kit (including known HCoV_s).¹¹ Further genomic sequencing of extracted RNA revealed sequences that matched with betacoronavirus lineage genomes, including > 85% identity with a previously published bat SARS-like CoV.

Later confirmed by whole genome sequencing and viral culture, the newly isolated virus initially was named 2019-nCoV.^{11,14} Although genetically distinct from SARS-CoV and MERS-CoV, it fell within the same genus. These studies were repeated and confirmed in samples from additional

Figure 1. Transmission Electron Micrographs of SARS-CoV-2 Virus Particles



Credit: NIAID-RML

patients from hospitals in Wuhan, with continued phylogenetic analysis providing further evidence that 2019-nCoV was more similar to bat-derived coronavirus strains than strains known to infect humans.^{15,16} The data suggested a bat reservoir for coronaviruses in general, including 2019-nCoV; however, the data also suggested that an intermediate animal (not a bat) may have been infected and amplified the virus in the Huanan Seafood Wholesale Market, although this remains incompletely understood.¹⁶

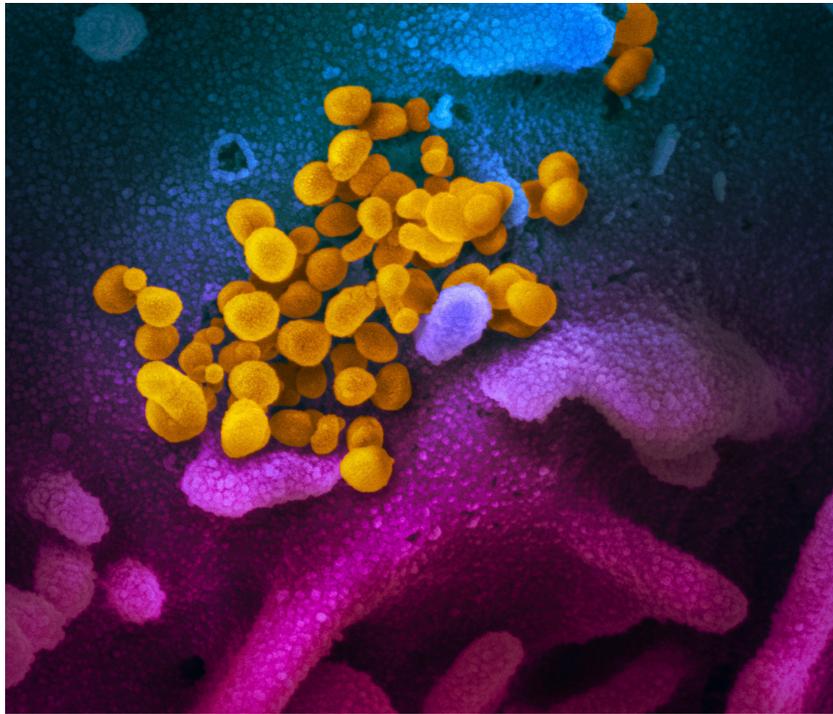
Similarly, SARS-CoV and MERS-CoV were believed to pass through other intermediate host animals.^{17,18} This raised further questions about the transmission of 2019-nCoV and its emergence as a human pathogen. One study suggested that a snake species may have been an intermediate host (based on similar codon usage) and two others implicated pangolins; however, neither hypothesis has been widely accepted, and further research is needed.¹⁹⁻²¹

Ultimately, by Dec. 31, 2019, the China CDC announced an outbreak investigation was underway, and by Jan. 1, 2020, it had closed the Huanan Seafood Wholesale Market.¹² This was followed by case investigation and

contact tracing by the China CDC. By mid-January 2020, as cases accrued and the natural history of the pneumonia of unknown etiology became clear, the China CDC announced the outbreak response had been upgraded to “Level 1,” the highest designation for such measures.¹² Meanwhile, the China CDC also had developed primers for molecular identification of the novel coronavirus disease and released the virus’s genetic sequence for distribution to health authorities globally. This ultimately served as a significant step forward for other nations to rapidly develop their own molecular identification assays.

Nevertheless, human-to-human spread was well underway, as cases in other provinces in China were reported by the end of January, and cases associated with travel to Wuhan were reported abroad in Southeast Asia.¹² On Jan. 22, 2020, the Chinese government issued a quarantine notice for the entire city of Wuhan, the center of the epidemic.²² However, at this point, outbreak containment was complicated by the Chinese New Year travel plans of many Chinese citizens, many of whom had traveled before the quarantine went into effect, as well as likely asymptomatic or mildly symptomatic

Figure 2. Novel Coronavirus SARS-CoV-2



This scanning electron microscope image shows SARS-CoV-2 (yellow) — also known as 2019-nCoV, the virus that causes COVID-19 — isolated from a patient in the United States, emerging from the surface of cells (blue/pink) cultured in the lab.
Credit: NIAID-RML

spread of the virus among the population at large.²³⁻²⁵

Several initial case series regarding the virus were published by late January 2020, providing the global community with a view into the epidemic and better delineating rates of severe disease, complications, and mortality among patients with confirmed infection.^{12,13,26} These studies emphasized that the burden of severe disease rested in particular with the elderly and those with comorbid conditions, but also provided early hints of the strain that healthcare facilities would face because of the need for drastic infection prevention measures, intensive care unit (ICU) support, and intensive ventilatory support measures, including extracorporeal membrane oxygenation. To alleviate these strains on the healthcare system, Chinese authorities undertook emergency measures of creating multiple facilities strictly dedicated to cohorting hundreds to thousands of COVID-19 patients, some of which were field hospitals constructed within days.²⁷

The number of confirmed cases rose rapidly throughout February 2020, with Chinese cases numbering into the tens of thousands. WHO member states discovered and reported cases in rapid succession, frequently associated with travel from East Asia, but with many indicative of community spread within their borders. On Feb. 11, 2020, WHO announced that the label “COVID-19” should be applied to the new disease in an effort to avoid stigmatizing regions where it had been first identified.³ By Feb. 29, 2020, more than 85,000 cases had been identified among 54 countries, with the vast majority of confirmed cases (79,000) within China.²⁸

Although sporadic clusters had appeared globally up to this point, Iran and Northern Italy faced sudden surges of COVID-19 patients in late February and early March 2020.²⁹ Italian ICUs reported attempts to cohort hundreds of COVID-19 cases, but still were forced to transfer patients to unaffected regions to cope with the massive numbers of critically ill patients.³⁰ Within

the first two weeks of March 2020, COVID-19 patients were estimated to occupy more than 1,000 ICU beds out of a total of 5,200 in Italy, and intensivists were left to consider implementing triage principles (denying lifesaving care to the sickest and least likely to survive) when allocating ventilatory support.^{31,32} In the meantime, multiple European countries reported increasing numbers of COVID-19 patients, while China’s extreme efforts at containment and quarantine had interrupted community transmission of new cases, thus shifting the center of the epidemic to the Western hemisphere.³³ On March 11, 2020, WHO elevated COVID-19 to “pandemic” status.³⁴

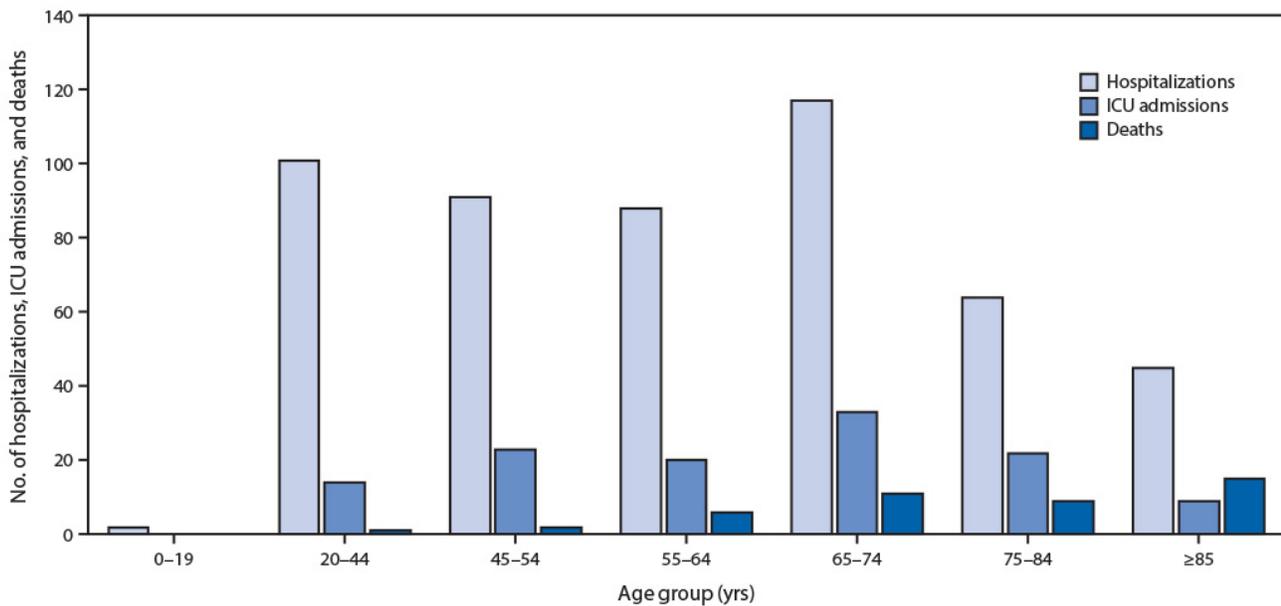
The United States began to see widespread community transmission in mid-March 2020, as patients began to number into the thousands and every state and U.S. territory reported cases.³⁵ Mirroring European and Chinese efforts to curtail community transmission, U.S. authorities enacted closures of universities, school districts, bars, restaurants, gyms, and other locations of public gathering, while millions of Americans were asked to work from home or to forsake working altogether.³⁶ At the time of this writing, the number of documented cases outside of China has overtaken those reported from within China, and global spread is recorded in more than 150 countries, with the number of new cases rising exponentially each day.³⁷

Epidemiology and Risk Factors

The epidemiology and risk factors for COVID-19 are evolving. Providers, healthcare systems, and governments are attempting to elucidate this information as the number of cases continues to rise.

Initially, the risk factors for acquisition of the disease were understood to be focused around exposure to a possible mammalian host at the Huanan Seafood Wholesale Market; however, later investigation questioned whether the disease may have presented first in the community, because neither the first identified case nor 13 other initial patients visited the market in question.¹³ As the infection spread, it

Figure 3. Coronavirus Disease 2019 (COVID-19) Hospitalizations,* Intensive Care Unit Admissions,† and Deaths,§ by Age Group — United States, February 12–March 16, 2020



* Hospitalization status missing or unknown for 1,514 cases.

† ICU status missing or unknown for 2,253 cases.

§ Illness outcome or death missing or unknown for 2,001 cases.

Source: U.S. Centers for Disease Control and Prevention. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) — United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:343-346. doi: <http://dx.doi.org/10.15585/mmwr.mm6912e2>

became clear that epidemiologic exposure to the seafood market alone could not explain all cases. Initial concern for human-to-human transmission was noted in the same study, based on known characteristics of the coronavirus group. Further studies described transmission of the virus among close contacts, including both family clusters and business contacts, suggesting the potential for index cases to transmit the disease asymptomatically.^{23,38} Since then, SARS-CoV-2 has been detected widely in individuals with no travel history or known contact with other individuals who have tested positive, confirming community spread of the virus. In addition, it is estimated that upward of 86% of cases in Wuhan prior to Jan. 23, 2020, were undetected, suggesting the pandemic is driven largely by asymptomatic spread or is spread by those with mild symptoms.²⁵

It also should be noted that some data have suggested that healthcare workers can become disproportionately represented among COVID-19 cases, likely due to the virus's potential for nosocomial spread.^{39,40}

The incubation period, defined as the period between exposure to the infection and the appearance of first symptoms, has been suggested as an average of five to six days, based on initial reports from SARS-CoV-2 and mirrored by other coronavirus diseases, including SARS and MERS.⁴¹ The range may extend to two to 14 days.

Disease severity and mortality are highest among the elderly.^{40,42} Individuals with comorbidities like hypertension, diabetes, and heart disease tend to be overrepresented among confirmed cases.^{12,13,26,43} U.S. data have estimated mortality rates to be highest among those older than 85 years of age (10% to 27%), followed by those aged 65 to 84 years (3% to 11%), those aged 55 to 64 years (1% to 3%), and least among those aged 20 to 54 years (< 1%).⁴² Providers should take note that even among nongeriatric adults, hospitalizations and ICU admissions still are common, especially among those with underlying conditions. (See *Figure 3 and Table 1.*)

Overall disease incidence among pediatric patients has been difficult

to assess, as each affected region has followed different approaches to testing populations. In one of the largest datasets from China (including 72,314 patients), only about 2% of documented cases occurred in patients younger than 19 years of age (965 patients).⁴⁴ Initial reports from Italy demonstrated that out of 22,512 cases, only 1.2% (70 cases) were documented among patients younger than 18 years of age, and there were no reported deaths in this age group.⁴⁰ Recent data described 4,226 cases in the United States and noted that only 5% of documented cases occurred in patients younger than 19 years of age (123 cases).⁴²

Further features of identified pediatric patients have been reported variably. The China CDC detailed features of 2,143 cases, of which 34% had a positive real-time polymerase chain reaction (RT-PCR) test and 66% were suspected cases (high risk by exposure to a known COVID-19 case with clinical symptoms, laboratory features, or imaging findings).⁴⁵ However, these data were limited somewhat because

Table 1. Hospitalization with and Without Intensive Care Unit (ICU) Admission, by Age Group Among COVID-19 Patients Aged ≥19 Years with and Without Reported Underlying Health Conditions — United States, February 12–March 28, 2020*

Age Group (yrs)	Hospitalized Without ICU Admission, No. (% Range [†])		ICU Admission, No. (% Range [†])	
	Underlying condition present/reported [§]		Underlying condition present/reported [§]	
	Yes	No	Yes	No
19-64	285 (18.1–19.9)	197 (6.2–6.7)	134 (8.5–9.4)	58 (1.8–2.0)
≥ 65	425 (41.7–44.5)	58 (16.8–18.3)	212 (20.8–22.2)	20 (5.8–6.3)
Total ≥ 19	710 (27.3–29.8)	255 (7.2–7.8)	346 (13.3–14.5)	78 (2.2–2.4)

* Includes COVID-19 patients aged ≥19 years with known status on underlying conditions.

[†] Lower bound of range = number of persons hospitalized or admitted to an ICU among total in row stratum; upper bound of range = number of persons hospitalized or admitted to an ICU among total in row stratum with known outcome status: hospitalization or ICU admission status.

[§] Includes any of the following underlying health conditions or risk factors: chronic lung disease (including asthma, chronic obstructive pulmonary disease, and emphysema); diabetes mellitus; cardiovascular disease; chronic renal disease; chronic liver disease; immunocompromised condition; neurologic disorder, neurodevelopmental, or intellectual disability; pregnancy; current smoker; former smoker; or other chronic disease.

Source: Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 — United States, February 12–March 28, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:382–386. doi: <http://dx.doi.org/10.15585/mmwr.mm6913e2>

of the overrepresentation of suspected cases, especially since this time period overlapped with influenza and respiratory syncytial virus season. Among these children, the median age was 7 years, with the age range from 1 day to 18 years. Biological males and females were represented equally. The majority of cases (> 90%) were asymptomatic or of mild to moderate severity; however, it was observed that more critical features were observed in children younger than 1 year of age (involving acute respiratory distress syndrome or respiratory failure with possible additional features of end organ dysfunction). There are no current comprehensive data to suggest which comorbidities in children increase the risk of severe disease. The authors of one study found that those who required an ICU stay and mechanical ventilation had coexisting conditions, such as hydronephrosis, leukemia, and complicated intussusception.⁴⁶

Pathophysiology and Transmission

The pathophysiology of coronavirus infections has been characterized largely by studies of the milder human coronaviruses and SARS-CoV. Human coronaviruses HCoV-NL63 and SARS-CoV both enter host cells

through interaction with human angiotensin-converting enzyme 2 (ACE2), which is found throughout the body, including the respiratory and GI tracts. It is thought that ACE2 normally has a protective role in the inflamed lung, and as such, SARS-CoV's interaction with this may contribute to disease severity.⁴⁷ The newly identified coronavirus, SARS-CoV-2, shows structural similarity to SARS-CoV in the receptor binding domains, which suggests that this new virus also binds at ACE2 sites.¹⁵ ACE2 is found primarily in the lower respiratory tract instead of the upper, which may account for why proportionally fewer patients have presented with symptoms of typical upper respiratory tract infection.⁴⁸ Upon infection of alveolar epithelial cells, the virus may cause cell lysis and sloughing of the respiratory epithelium. Similar to other viral infections, it is thought that the host response is responsible for many of the disease manifestations. In studies of SARS-CoV, researchers have suggested that damage to the lungs of infected patients occurs both directly, by viral destruction of alveolar and bronchial epithelial cells and macrophages, and indirectly, through production of immune mediators, although the exact role of these mechanisms remains controversial.⁴⁹

Viral transmission of the known human coronaviruses (HCoVs 229E, OC43, NL63, and HKU1) has not been well studied. Based on the behavior of other respiratory tract viruses, coronaviruses are believed to spread mainly through respiratory droplets, along with direct and indirect contact with infected persons.⁶ SARS-CoV primarily was transmitted directly through mucous membrane contact with infectious respiratory droplets, as well as through exposure to fomites, with most cases occurring in people who had close contact with those affected by the illness.⁵⁰ It has been established previously that both SARS-CoV and SARS-CoV-2 use ACE2 to enter cells; the presence of the receptor in the GI tract has led to questions regarding fecal-oral spread of the virus. In a study of 73 patients hospitalized with COVID-19 (ages 10 months to 78 years), investigators found that 53% of patients had a stool positive for SARS-CoV-2 RNA. Notably, 17 patients continued to demonstrate positive stool RNA after developing negative respiratory samples.⁵¹ Further studies have looked for evidence of live virus in stool samples with mixed results.^{52,53} The Report of the WHO-China Joint Mission on COVID-19 did not identify the fecal-oral route

as a main driver of SARS-CoV-2 transmission.⁵⁴

Airborne spread has not yet been reported; however, the authors of one study in laboratory conditions suggested that aerosol transmission of the virus is plausible, with a similar aerosolized stability to that of SARS-CoV.⁵⁵ In addition, fomite transmission via contaminated surfaces is believed to be a potential route of transmission, with results of one study demonstrating stability of potentially viable virus on surfaces like plastic and stainless steel for up to 72 hours.⁵⁶

There have been concerns about vertical transmission of infection, especially after reports of infection detected in a 36-hour-old infant in China. This child's mother had tested positive by nasopharyngeal swab, but cord blood, placental specimens, and breast milk did not have the virus present.⁵⁷ In a later case series of nine pregnant women who tested positive for SARS-CoV-2 late in pregnancy, all delivered healthy infants via cesarean delivery and had negative testing of throat swabs, cord blood, amniotic fluid, and breast milk.⁵⁸ These findings were repeated in a larger series of 38 pregnant women and infants.⁵⁹ One case report has suggested that a neonate born to a mother with active COVID-19 developed an elevated immunoglobulin M (IgM) response to SARS-CoV-2, which is suggestive of vertical transmission because maternal IgM is not passed through the placenta, although the infant's nasopharyngeal RT-PCR results for the virus remained repeatedly negative.⁶⁰ Elevations in immunoglobulin G and IgM also have been reported among other newborns of mothers with COVID-19.⁶¹ Further investigation is warranted, but it remains unclear if vertical transmission is a significant mechanism of infection of neonates at this time.⁶²

Clinical Manifestations

The first described manifestations of COVID-19 in hospitalized adult patients were reported as "pneumonia of unknown cause."¹³ This was defined as an illness without a causative pathogen with clinical features

of fever ($\geq 38^\circ\text{C}$), radiographic evidence of pneumonia, low or normal white-cell count or low lymphocyte count, and no symptomatic improvement after antimicrobial treatment for three to five days following standard clinical guidelines; or as the first three criteria, plus an epidemiologic link to the Huanan Seafood Wholesale Market or a sick contact with similar symptoms.⁶³ Later reports described the most prominent early symptoms as fever (98% of patients), cough (76%), and myalgia/fatigue (44%).⁶³ Laboratory findings among adult patients included lymphopenia (83.2%), thrombocytopenia (36.2%), elevated C-reactive protein (60.7%), elevated lactate dehydrogenase (41%), and elevated aminotransferases (AST/ALT, 22.2% and 21.3%, respectively). More than 23% of patients had at least one coexisting illness. The presence of coexisting illness was more common among patients with severe disease than among those with non-severe disease (38.7% vs. 21%). Age also was a predictor of disease severity; patients with severe disease were a median of seven years older than those with non-severe disease.

Pediatric patients diagnosed with COVID-19 have had somewhat more diverse clinical presentations, with a significant number of patients remaining asymptomatic, and far fewer patients with severe disease. It is important to note that the bulk of data describing clinical symptoms in pediatric populations are from hospitalized children in China. Fever has been reported in 41% to 65% of cases and cough in 38% to 65% of cases.^{41,46,64,65} Features of upper respiratory infection have been less prevalent, reported at 15% to 19%, with pharyngeal erythema specifically identified in 46% of cases.^{46,65} As noted previously, the virus has the ability to infect the GI tract; however, few pediatric patients presented with GI symptoms: 8% to 15% were noted to develop diarrhea and 6% to 10% to develop vomiting.^{46,64,65}

Few pediatric patients have severe manifestations. Three severe cases were described in one large review of 171 children with COVID-19; all three

had coexisting conditions (hydronephrosis, leukemia on maintenance chemotherapy, and intussusception), and ultimately the child with intussusception had multi-organ failure, which resulted in death.⁴⁶ Although further pediatric deaths have been reported, details of the patients have not been adequately clarified to determine if specific risk factors were present.

There have been several additional reports focusing on infants and neonates. A case series of hospitalized infants only included nine cases in China (age 28 days to 1 year), with the youngest being just 1 month of age. All had a sick family contact, and none experienced severe complications or required intensive care treatment. Of these cases, four had fever, three others had mild disease or no symptoms, and the last two had an unknown presentation.⁶⁶ A later case series of four neonates born to mothers with known COVID-19 showed no manifestations of disease in any neonate. Three of the four patients' parents consented to testing and tested negative.⁶⁷ One of the largest studies on pediatric patients described an increased severity of disease in infants younger than 1 year of age; however, more than 70% of these patients were diagnosed on clinical symptoms alone, without SARS-CoV-2 testing to verify suspected COVID-19 disease.⁴⁵

Rates of asymptomatic infection have been reported as high as 13% to 23%.^{46,64} It is likely that early in the epidemic's investigation, many children who were tested were known contacts of a positive case. Of children represented in the data, 65% to 90% had a close contact who tested positive or were part of a family cluster.^{46,64,65,68}

Laboratory findings among pediatric patients have been variable. The authors of a review article focused on pediatric laboratory findings in COVID-19 found a normal leukocyte count in almost 70% of patients, while only 15% of patients mounted leukocytosis.⁶⁹ Leukopenia is more variable, reported in 5% to 26% of cases.^{46,69} Procalcitonin was found to be elevated in 64% of patients in one large case series of SARS-CoV-2 positive children ($n = 171$).⁴⁶ However, smaller

studies have demonstrated lower percentages of children with elevated procalcitonin.

Radiographic findings on chest X-ray or chest computed tomography (CT) are common among individuals with COVID-19, and even those with asymptomatic or mild disease may have abnormalities suggestive of infection. Among adult and pediatric patients with disease, 75% to 98% are reported to have evidence of pneumonia on imaging, particularly with bilateral lobular and subsegmental consolidations described on CT scans, as well as multifocal ground glass opacities.^{12,26,65} Pediatric patients also may demonstrate consolidation with a surrounding halo sign.⁶⁵ Overall, pediatric patients with COVID-19 are less likely to have fewer findings on CT, and lesser extent of disease on radiography.⁷⁰

Diagnosis and Testing

In mid-January 2020, the China CDC developed primers for molecular identification of the novel coronavirus disease and released the virus's genetic sequence for distribution to global health authorities.¹² This was an important contribution to the global health community, allowing other nations to rapidly develop their own molecular identification assays to track and control new cases abroad.

Using these sequencing data, new cases in the United States are diagnosed primarily based on RT-PCR testing, available through multiple commercial laboratory suppliers under the Emergency Use Authorization of the Food and Drug Administration (FDA).⁷¹ Viral genetic material has been detected in bronchoalveolar lavage fluid, sputum, nasal and pharyngeal swabs, bronchoscope brush biopsies, feces, and blood, while urine appears to be routinely negative.⁵³ For the time being, the U.S. Centers for Disease Control and Prevention (U.S. CDC) recommends collecting nasopharyngeal swabs as the preferred choice for initial diagnostic testing, with oropharyngeal, nasal mid-turbinate, and anterior nares swabs as acceptable alternatives.⁷² Collection of sputum is an option for patients with

productive cough, although sputum induction is not recommended.

Local and national test reagents and infrastructure have been outpaced by spreading community transmission and local surges of cases. Although tests remain scarce, the U.S. CDC recommends prioritizing testing according to the following categories of patients:⁷³

- hospitalized patients and symptomatic healthcare workers;
- symptomatic patients in long-term care facilities, symptomatic patients aged 65 years and older, symptomatic patients with underlying conditions, and symptomatic first responders;
- symptomatic critical infrastructure workers; individuals who are not any of the above but present with symptoms; and mildly symptomatic individuals in communities with high COVID-19 hospitalizations.

Testing for other pathogens also should be performed during initial evaluation, but codetection between SARS-CoV-2 and other respiratory viruses has been reported.⁷⁴ In one small study of pediatric patients with SARS-CoV-2, coinfection with other respiratory pathogens (namely influenza A and B, mycoplasma, respiratory syncytial virus, and cytomegalovirus) was found in 40% of patients.⁶⁵ Thus, the presence of influenza or other respiratory pathogens does not rule out COVID-19, and the U.S. CDC recommends that specific testing for SARS-CoV-2 should not be delayed.⁷²

In one analysis of patients who underwent serial RT-PCR tests and serial chest CT scans, the sensitivity of an initial CT scan at presentation was estimated to be upward of 97%, albeit with greater accuracy in patients older than 60 years of age.⁷⁵

Management

At the time of this writing, there is no FDA-approved drug specific for treating COVID-19.⁷⁵ Emphasis currently is placed on supportive care of complications, as well as strict infection control practices. Many individuals with COVID-19 will be able to manage their illness on their own at

home, which may be preferable as a means of case isolation. However, some patients may have progression of symptoms to moderate or severe disease, especially older individuals with cardiovascular disease, renal disease, diabetes, or immunocompromising conditions. The decision to admit and monitor patients at higher risk for severe complications must be made at the discretion of the provider on a case-by-case basis. Patients with COVID-19 who are discharged home should be warned that increasing shortness of breath or worsening symptoms may require re-evaluation by a healthcare provider.

Current guidelines from the U.S. CDC emphasize that corticosteroids may be harmful and should not be given when managing COVID-19 infections, unless otherwise indicated by another condition.⁷⁵ This recommendation is based on data from other coronavirus outbreaks (SARS and MERS) and influenza studies that demonstrated that corticosteroid use could prolong viral replication in patients and ostensibly delay or hamper recovery.^{75,76}

Multiple other medications are under investigation or consideration as potential therapies for COVID-19 infection. Recently, chloroquine and hydroxychloroquine (already approved by the U.S. FDA for other uses) have been cited as promising therapies, although their ultimate benefit remains unknown.⁷⁷ Their method of action is believed to be based on alteration of phagolysosome pH in human cells, thus interfering with SARS-CoV-2's (or any intracellular organism's) ability to reproduce within host cells.⁷⁸ In vitro testing supported this rationale, and 20 clinical studies were launched at multiple Chinese hospitals to evaluate the efficacy of chloroquine in COVID-19.^{78,79} Some investigators have claimed the initial data demonstrated that chloroquine may reduce patients' length of stay and ameliorate the progression of COVID-19 pneumonia,^{78,79} but this remains controversial. In another study, investigators claimed that the combination of hydroxychloroquine and azithromycin led to a reduction

of viral load in COVID-19 patients, but this study was nonrandomized and extremely small.⁸⁰ Thus, there are no U.S. recommendations at the time of this writing to use these agents in COVID-19 patients.

Several other medications already marketed as antivirals also are under consideration for the treatment of COVID-19. Remdesivir is a nucleoside analogue previously used in Ebola treatment (albeit with no improvement in outcomes compared to placebo), but in vitro data support its efficacy against a variety of coronaviruses.^{81,82,83} Lopinavir and ritonavir (Kaletra) are protease inhibitors with some data supporting their efficacy against SARS and MERS, but recent data in the current COVID-19 pandemic suggest they are not useful.⁸⁴⁻⁸⁶ Darunavir/cobicistat also are protease inhibitors considered in the treatment of COVID-19, but there are no in vitro or clinical data to support their use at this time.⁸⁷ Ribavirin is another nucleoside analogue that has been considered; however, it was found to have little effect on outcomes in SARS and MERS.^{84,88}

Other therapies considered in the treatment of COVID-19 include tocilizumab (interleukin-6 inhibitor)⁸⁹ and aerosolized alpha-interferon,⁹⁰ but there are no recommendations from the U.S. CDC to use these therapies. The FDA is facilitating access to convalescent serum/plasma (antibodies harvested from COVID-19 survivors) as an investigational therapy,⁹¹ but with significant side effects and no firm evidence to support its efficacy against COVID-19, there is no recommendation for its use at this time.

Recently, there has been discussion of whether angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) increase the risk of infection and severity of COVID-19, primarily because of SARS-CoV-2's previously described mechanism of binding to ACE2 to facilitate cell entry.⁹² No evidence has been found to support this hypothesis, and on the contrary, some animal studies suggest these medications actually may be protective against severe disease. At this

time, discontinuation of these medications in COVID-19 disease is not recommended.

Likewise, because SARS-CoV-2 binds to ACE2, some have suggested that medications that lead to upregulation of this enzyme, such as nonsteroidal anti-inflammatory drugs (NSAIDs), could lead to more severe disease.⁹³ This supposition was followed by statements from the French Ministry of Health that patients with COVID-19 should avoid NSAIDs.⁹⁴ However, at this time there is no published clinical evidence to recommend discontinuation or avoidance of NSAIDs in COVID-19 patients.⁹⁵

Infection Prevention and Precautions

Strategies to prevent community and nosocomial spread of COVID-19, as well as to minimize exposure of at-risk populations, are paramount. The U.S. CDC has provided comprehensive, updated recommendations for community mitigation strategies aimed at slowing the transmission of COVID-19 and reducing illness and death, while minimizing social and economic impacts.⁹⁶ For all individuals, it is recommended people avoid close contact with others; avoid touching the eyes, nose, and mouth; and clean hands frequently, either using soap and water for 20 seconds or using hand sanitizer that is at least 60% alcohol.⁹⁷

Because of the known problem of asymptomatic spread, recommendations have expanded beyond the simple message of staying home when symptomatic to practicing “social isolation.” On an individual level, this includes encouraging individuals to maintain a distance of three to six feet apart from each other. On a larger scale, this has led to the systematic closure of schools, businesses, gymnasiums, restaurants, and bars, and the cancellation of large community events. There have been calls for widespread community quarantine, recommending that all individuals “shelter in place” and avoid all possible interaction with others.

The U.S. CDC recommends minimizing potential healthcare exposures

to contagious cases of COVID-19 through a variety of tactics,⁹⁸ including the following:

- asking patients with symptoms of cough, sore throat, or fever to reschedule appointments for routine care;
- using telehealth and telephone triage protocols to determine if symptomatic patients can be managed from home;
- requesting patient transport and emergency medical services to contact receiving emergency departments on transport protocols of symptomatic patients;
- limiting points of entry to health-care facilities, and posting visual materials and handwashing/sanitizer stations at these points, as well as throughout hallways;
- enforcing cough etiquette and studious masking of all symptomatic patients;
- designating separate waiting areas for patients with respiratory symptoms in coordination with the facility's infection prevention specialists;
- ensuring patients in such waiting areas are separated by at least six feet;
- ensuring patients with respiratory symptoms (including suspected or confirmed COVID-19) are transported and triaged efficiently and quickly through specially designated areas.

There is no approved vaccine available for the prevention of COVID-19 at this time. The discovery and production of such a vaccine is a national and international public health priority to control the pandemic. Recently, the U.S. National Institutes of Health has initiated a Phase I clinical trial of an investigational vaccine.⁹⁹ Efforts to produce a vaccine also are underway in China and Europe.¹⁰⁰

Personal Protective Equipment

As in all situations in which a patient presents with a potentially contagious infectious disease, practitioners confronting potential cases of COVID-19 should contact their institutional infection prevention

specialists for specific guidance. In general, the U.S. CDC recommends that all healthcare personnel entering the room of a patient with known or suspected COVID-19 use a respirator or facemask, gown, gloves, and eye protection.⁹⁸ Staff should ensure they follow personal protective equipment (PPE) donning and doffing procedures correctly to ensure contaminated droplets are not passed onto the hands, face, or eyes.¹⁰¹

Conclusion

The final costs and outcomes of the COVID-19 pandemic cannot be predicted, but its current implications are historic in scope. Some efforts at modeling the pandemic have predicted that without appropriate action, millions of lives could be lost in the United States and Europe.¹⁰² Healthcare workers already are tasked with extremely high patient volumes in heavily impacted regions, and many have become separated from their families for the sake of isolation and protecting the vulnerable. There are few, if any, individuals in the world who will not have some personal connection to this pandemic.

However, while anxieties and doubts multiply in the face of such grave predictions, providers should remind themselves that this pandemic ultimately will pass. Although the immediate effects of COVID-19 may seem overwhelming, the courage and efforts of healthcare workers will outlast the disease. Indeed, the day may not be so distant when this pandemic is relegated to mere historical interest, and humanity will have learned an essential lesson in vigilance against infectious diseases.

Acknowledgement

The authors would like to extend their appreciation to Anne Blaschke-Bonkowsky, MD, PhD, for her support and advice throughout the writing of this manuscript.

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CME/CE Questions

1. A previously healthy female with recent onset of tactile fevers, rhinorrhea, cough, and congestion is brought to your facility. Overall, she is well-appearing, well-hydrated, and breathing comfortably, albeit with intermittent coughing. A respiratory viral panel is sent and comes back positive for HCoV NL63. The patient has never heard of this and is very worried. How do you counsel her on next steps?
 - a. Since the patient tested positive for a coronavirus, she is at risk of severe complications and should be admitted for monitoring and respiratory support.
 - b. As HCoV NL63 is a common cause of cold symptoms, she should continue supportive care at home and be given return precautions.
 - c. Since the patient tested positive for a coronavirus, the family should be tested and quarantined.
 - d. A CT scan of the chest can help determine if she is at risk of severe complications.
2. You are on a hospital committee developing clinical guidelines for testing and diagnosis of children with COVID-19. Which of the following statements represents accurate information that should be taken into account?
 - a. Most pediatric patients presenting with fever have COVID-19.
 - b. Even children with a known close contact with COVID-19 are unlikely to have it.
 - c. Pediatric patients with COVID-19 have varied clinical presentations, with proportionally more patients with asymptomatic or mild to moderate disease.
 - d. Rashes are a common feature of COVID-19 infection.
3. A male with chronic renal disease presents with fever, cough, and shortness of breath. His oxygen saturation on room air is low at 85%, and he is quickly placed on 1 liter per minute of supplemental oxygen. You order a COVID-19 nasopharyngeal swab polymerase

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chain reaction test, but you do not expect to have results for at least 24 hours. In the meantime, you order some basic laboratory studies.

Which of the following laboratory values would be consistent with COVID-19 infection?

- a. Low lymphocyte count
 - b. Elevated C-reactive protein (CRP)
 - c. Elevated aminotransferases (AST/ALT)
 - d. All of the above
4. While evaluating the man from question 3, you also obtain plain X-rays and computed tomography of the chest. Which of the following radiographic findings would be consistent with COVID-19 infection?
 - a. Mediastinal lymphadenopathy
 - b. Isolated unilateral pleural effusion
 - c. Bilateral, multifocal ground glass opacities
 - d. All of the above

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PRIMARY CARE REPORTS™ (ISSN 1040-2497) is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Primary Care Reports*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

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GST Registration No.: R128870672

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