Coronavirus Infections: COVID-19 (SARS-Cov-2)

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Purpose

The purpose of this course is to provide current information about the coronavirus COVID-19 (SARS-CoV-2) and the history of the recent COVID-19 pandemic and the signs and symptoms, complications, transmission precautions, diagnosis, and treatment.

Goals

Upon completion of this course, the nurse should be able to

- Describe the coronavirus, including appearance.
- Discuss the history of severe coronavirus infections.
- Describe the role that wet markets have in spreading zoonotic diseases to humans.
- Explain the history of COVID-19.
- Discuss transmission concerns for COVID-19.
- Discuss at least 10 common symptoms of COVID-19.
- Describe at least 5 major complications of COVID-19.
- Discuss treatment options for COVID-19.
- Discuss at least 2 types of medications that may be used for COVID-19
- Discuss prevention measures for COVID-19

Introduction

The news about coronavirus COVID-19 (SARS CoV-2) pandemic remains grim even though the worst seemed to be easing for a time until a recent upsurge in cases.

During the peak of the current outbreak, healthcare providers were

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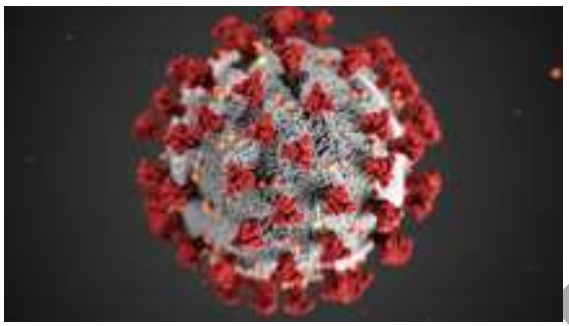
exhausted and at high risk of infection. Hospitals were overwhelmed and out of ventilators and PPE. Convention centers were being converted to hospitals. Field hospitals were being set up in parks. Navy hospital ships were anchored at New York City and Los Angeles. Refrigerator trucks stood outside of hospitals to hold the dead. Stores were boarded up, and streets are vacant. People were—and still are--out of work and afraid.

Coronaviruses are not new. They have been around for aeons, infecting humans with mild upper respiratory infections, such as the common cold. Animals infected with coronaviruses may develop respiratory, gastrointestinal, liver and neurologic disease. Therefore, when these viruses jump from animal species to humans, severe illness and the risk of pandemics can result.



Coronaviruses are a group of viruses and are so named because of their shape, which is round with a halo of proteins spiking from the surface. Coronaviruses are composed of RNA, and each variety can be very distinct from others. There are four primary type of coronaviruses: alpha, beta, delta, and gamma. Four varieties (229E, NL63, OC43, and HKU1) cause up to 30% of common colds.

Coronaviruses first came to the attention of the public in 2002. In November 2002, the first case of a new type of coronavirus infection occurred in Guangdong Province, China, resulting in the death of the patient, followed by more infections, but the Chinese government failed to report the outbreak to the WHO or to acknowledge that an outbreak was occurring, even though the WHO requested information in December based on internet reports of a "flu outbreak." When, several months later, the WHO was able to take action, 500 people had died and over 2000 cases had occurred worldwide.

This new coronavirus infection was referred to as severe acute respiratory syndrome (SARS) and was a documented instance of a coronavirus jumping from wildlife to humans. By April, the CDC was able to publish the sequence of the virus.

The CDC issued a number of travel alerts (Toronto, Singapore, Toronto, China, Taiwan, Hong Kong (areas with outbreaks) in order to reduce risk to the United States. By July 2003, the outbreak was contained, but SARS had spread to 17 countries with 8096 identified cases and 774 deaths, a 9.6%

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mortality rate. Only 8 people in the United States became infected and all survived. It is estimated that the SARS outbreak cost the world about $40 billion dollars.

Subsequently, SARS has been followed by outbreaks of MERS and COVID-19, the coronavirus infection now ravaging the world.

How are wet markets implicated in transmission of coronaviruses in China?

Coronaviruses are zoonotic diseases (those that spread between animals and humans). In China, both SARS and COVID-19 have been linked to wet markets that sell fruits, vegetables, spices, live animals (pigs, chicken, ducks, civets, rats, beavers, porcupines) butchered meat, dogs, rabbits, fish, shellfish and snakes. The Chinese, especially, like to purchase live animals and have a penchant for wild animals, which many believe can cure disease and improve male potency.

The markets that sell this wide range of food products are called wet markets because workers slosh water about the floor to wash away the inevitable feces and urine, resulting in a literal soup of pathogens. Whether people become infected from contact with the animals or ingestion is not always clear. The SARS coronavirus infection was finally traced to civets (cat-like mammals), which had become infected from bats. There is strong evidence that COVID-19 originated in horseshoe bats and was transmitted to another animal that eventually transmitted it to humans.

There is evidence that COVID-19 can be transmitted to domesticated animals (dogs, cats) and captive animals (gorillas, snow leopards), and it has been found in wild minks, so there is concern that it could spread to more wild animals, mutate, and then transmit back to humans in a more virulent form.

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2019 novel coronavirus, COVID-19 (SARS-CoV-2)

As of August 31, 2020, more than 25 million cases of COVID-19 had occurred worldwide, resulting in over 850,000 deaths. By August 11, 2021, the number had increased to 204 million confirmed cases and about 4.4 million deaths. The pandemic that has spread throughout the world started out with a few cases in a city in China.

History

It began on December 31, 2019, when the Chinese authorities notified the WHO that several cases of pneumonia from an unknown virus had occurred in Wuhan (first cases in early December) and that several of the infected had been employed at the Huanan Seafood Wholesale Market (a wet market), which was closed down on January 1 although the animal implicated is not yet certain, but the virus is believed to have originally derived from a bat.

By January 7, a new coronavirus, then dubbed the 2019 novel coronavirus (2019-nCoV) or "Wuhan coronavirus" was identified. On January 22, Wuhan authorities banned the trade of live animals at wet markets. The first reported death occurred on January 9, but as of January 27, 81 people had died with the death toll increasing daily and 2800 cases recorded. Up until then, all deaths occurred in China.

On January 13, the first case outside of China occurred in Thailand in a woman who had come from Wuhan. While most cases occurred in China, by the end of January 2020, almost 10,000 cases of the coronavirus infection had been reported in 21 countries, including Australia, Cambodia, Canada, France, Japan, Malaysia, Nepal, Singapore, South Korea, Sri Lanka, Taiwan, Vietnam, and the United States. The first case in the United States was reported on January 20 in Snohomish County, Washington, in a man who had returned from Wuhan.

In an effort to curb spread of the disease, China blockaded a large area of the country, using the military to seal off the area, and travel advisories were in place from the CDC regarding travel to and from China. People in China were advised to wear face masks and to avoid unnecessary contact with others. Eventually, those infected in China were forced into quarantine centers, but the death rate continued to rise until late in February when it began to level out, suggesting that the drastic methods used to control the disease were having a positive effect.

On February 11, 2020, the WHO dubbed the novel coronavirus COVID-19 to discourage use of "Wuhan coronavirus" and identifying the coronavirus with China. The virus is officially now referred to as SARS-CoV-2.

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By March 30, 2020, China had 81,470 cases of COVID-19 with 3304 deaths (4% death rate), but China was surpassed by the United States, Italy, and Spain. As of August 31, 2020, China had reported a total of 85,379 infections and 4634 deaths, suggesting that the stringent lockdown was effective in slowing the progress of the disease.

South Korea also experienced a significant outbreak with 28 cases on February 15 increasing to 9661 by March 16 with 158 deaths (1.6% death rate). Korea instituted massive testing and isolation of those infected, and many authorities credit this with the fact that the death rate in Korea was lower than in other countries. Bu August 31, 2020, South Korea had reported a total of 19,947 total infection and 324 deaths. A year later, August 11, 2021, the total of infections reached 217,000 and deaths 2138.

Another cause for concern was an outbreak that occurred on the *Diamond Princess*, a cruise ship. On January 20, a passenger on the cruise ship disembarked in Hong Kong and was hospitalized with infection. By February 4 in Japan, an additional 10 passengers were diagnosed with coronavirus infection, and the Japanese placed the ship in quarantine with passengers confined to the ship.

Eventually, the passengers were evacuated to home countries or to hospital facilities in Japan, but by March 5, 696 passengers and crew (out of 3711) had become infected, and 7 died. This resulted in warnings about the danger of the infection spreading on cruise ships. As of March 30, the number infected on the ship had increased to 712 (19%) and 3 additional people had died for a total of 10 (1.4% death rate).

On January 26, 2020, the United States had confirmed 5 cases of COVID-19 from travelers. Subsequently, on January 31 the United States suspended entry of foreign nationals who had traveled in China in the previous 15 days. The first death outside of China occurred in the Philippines on February 2.

But it wasn't until February 29 that the United States recorded its first death from a patient near Seattle. The first deaths from COVID-19 were associated with the LifeCare Center nursing facility in Kirkland, Washington, and were also the first cases identified as resulting from community spread. At that time, 52 patients and staff were also showing symptoms. (As of March 21, 35 deaths were linked to that facility alone.)

On March 11, the WHO formally declared the COVID-19 outbreak a pandemic with 114 countries (at that date) recording infections.

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By March 30, COVID-19 virus was present in all 50 states in the United States. Cases were beginning to soar: on March 16 there were 4598 confirmed cases and 86 deaths. As of March 30, 2020, the United States had 163,470 cases and 3148 deaths (1.9% death rate), but the cases were literally increasing hourly. By August 31, 2020, over 6 million cases had occured and over 185,000 deaths. By August 2021, one year later, almost 37 million coronavirus cases had occurred with about 617,000 deaths.

The United States has had the most cases and the highest death count of any other country in the world (followed by Brazil and India), and the reasons for that (inadequate response, conflicting messages, confusion, distrust of authorities, conspiracy theories) will likely be debated for many years.

Identification of active cases was hampered by problems with testing in the United States. While Europe used a test developed in Germany and distributed through the WHO, the United States decided the CDC should develop its own test, but the original tests that were shipped were defective, and the supply of tests has been (and often continues to be) inadequate and unevenly distributed.

In response to the severity of the pandemic, individual states, cities, and counties implemented restrictions, including self-isolation/stay at home. Schools closed across most of the United States in March and April and all but essential businesses closed in most states. Stay at home orders were the norm and people were urged to maintain distance from others and to wear facemasks when in public.

The death rate varies widely from one country to another, and the reason for that is not yet totally clear but may have to do with testing capabilities and availability of ICU beds and ventilators as well as the age of the patients. South Korea, for example, had a high rate of infections in younger adults while Italy had a high rate of infections in older adults. Another factor is that death usually occurs 2 to 4 weeks after the onset of symptom, so the number of deaths continues even if the rate of infection slows.

Vaccinations first became available in the United States for older adults in December 2020 and gradually rolled out over 2021 until by summer vaccinations were free and available to all those 12 and older. Vaccines are currently available from Moderna (2 injections), Pfizer (2 injections), and Johnson & Johnson (1 injection). Third world countries have lagged far behind in accessibility to vaccines.

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While the CDC and scientists have stressed the importance of vaccinations to control the spread of the disease, a campaign of misinformation and conspiracy theories, spread through the media, has resulted in large numbers of the population refusing to be vaccinated. Some states (Arkansas, Texas, Florida) have passed laws to preclude requiring people to be vaccinated or wear masks.

As of August 2021, 49.6% of the entire US population is fully vaccinated (58.1% of those eligible). Vaccination rates, however, vary widely across the country. For example, 68% of people in Vermont are vaccinated but only 38.6% of people in Mississippi.

The CDC is now recommending that all pregnant women receive the COVID-19 vaccination as studies have indicated that is safe for the mother and fetus. Clinical trials are evaluating the effectiveness of the vaccines for children under age 12.

Now, even though the death rate is a concern, states have phased in reopening. Increasingly, people who have been untouched by the coronavirus are appearing in public in groups and without masks, increasing concern that the death rate will begin to spiral out of control. Subsequent increases in caseload have caused some states to retrench and reimpose some lockdowns, especially of high risk venues such as bars and restaurants.

Variants: The coronavirus has continued to mutate. The alpha variant was first identified in the United Kingdom and detected in the United States at the end of 2020 and resulted in increased severity of disease and increased fatalities. The beta variant, first identified in South Africa, was detected in the United States by January 2021.

Numerous other variants have also been detected and are considered variants of concern. However, the variant of greatest concern at present is the delta variant, identified in India and detected in the United States by March 2021. This variant appears to be much more virulent than previous variants and has spread rapidly throughout the world, including in the United States, where it is now the predominate variant. A delta plus variant has recently been detected as well and may be even more transmissible.

Recent studies suggest that those infected with the delta variant have about 1000 times more virus in their respiratory systems than with the original variant, and the coronavirus spreads up to 250 times more rapidly. So far,

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the vaccinations seem to be effective in preventing most cases of severe disease and death from the delta variant.

In the early days of the delta variant, infections were primarily contained to areas with low rates of vaccination, but recently infections are increasingly occurring at high rates in areas with high rates of vaccinations, fueled by the unvaccinated and the ability of the delta variant to infect those who are fully vaccinated and who can then readily infect others.

It's important to note that while most patients who died initially from COVID-19 were older adults, especially those with underlying health problems, people of all ages are at risk. Children, who were thought essentially exempt, are developing severe illness, and some have died. The delta virus seems to be infecting greater numbers of pediatric patients. Hospitals that had emptied of COVID-19 patients have begun to fill again, and some hospitals have reached capacity. At present, most cases of severe COVID-19 and death are among the unvaccinated or immunocompromised.

Incubation

Much is still not known about the disease, but the incubation period appears to be about 10 to 14 days with many showing symptoms by day 5. Many are infected but asymptomatic, and this poses a serious problem for transmission.

Duration of infectivity

The CDC states that those who are infected should isolate from others until 10 days after onset of symptoms AND at least 24 hours without fever AND improvement in other symptoms for mild to moderate infections but up to 20 days for severe infections.

Signs and symptoms

Much information about Covid-19 still comes from journalists and is anecdotal rather than from medical researchers because of the newness of the virus, but new information is appearing almost daily.

Presentation is similar to SARS with most presenting at onset with:

- Fever (77–98%):
- Cough (46%–82%)
- Myalgia or fatigue (11–52%)
- Shortness of breath (3-31%)
- Chills

Other common symptoms include:

- Loss of taste and smell (an early symptom).

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- Hemoptysis
- Nausea
- Diarrhea
- "Red eyes," conjunctivitis.
- Hallucinations (associated with fever)
- Confusion
- Rash, hives.

Some patients, such as the very young, very old, and immunocompromised may not exhibit fever. Others may develop sore throat, headache, sputum production, hemoptysis, nausea, and diarrhea. Healthcare workers are reporting that diarrhea is common, with or without respiratory symptoms. A study in the UK indicated that an early sign of COVID-19 infection is a sudden loss of taste and smell even though no other signs may be initially present.

Older patients may initially exhibit loss of appetite, weakness, lethargy, and a functional decline (falls, difficulty walking), and some may experience altered mental status (confusion, agitation). Atypical symptoms become more common with advancing age, occuring in 31% of those 65 to 74 and 44% of those over 85. Patients that present with atypical symptoms may become quite ill and up to a third die, but they often have fewer respiratory symptoms and usually do not require ventilation.

Some patient present with only GI symptoms, nausea and diarrhea. Patients with severe disease can progress to severe bilateral interstitial pneumonia, the most common cause of death. Additionally, patients who seem to have mild disease may take a sudden turn for the worse, and patients who have been ill and then show improvement may rapidly decompensate within hours.

Patients may test negative even with symptoms and then later convert to positive. Some patients who tested negative after having COVID-19 infection later test positive again. Reports of reinfection were primarily anecdotal; but in August 2020, four cases (including one in Nevada) were documented. The patient in Nevada was found to be infected with a different strain of the virus than with the initial infection. Reinfection continues to occur.

Children still tend to have milder symptoms than adults although one study suggests that infants and young children are at increased risk of developing pneumonia.

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Pneumonia: At present the most common complication is pneumonia, bilateral interstitial pneumonia. Patients may present with pneumonia or may have milder symptoms that progress. Patients may develop severe respiratory distress very rapidly, within hours.

Symptoms of pneumonia typically develop about 8 to 9 days (5-13) days after onset. Up to 29% of hospitalized patients develop acute respiratory distress syndrome. About half of those with critical illness die.

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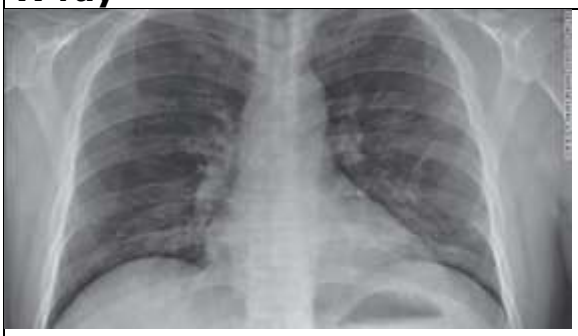	

The CT and x-ray show ground glass opacities. The CT is more sensitive and may detect abnormalities earlier. Post-mortem exams show these areas fill with mucous that prevents oxygen exchange and accounts for the increasing dyspnea.

Other complications may include cardiac injury, arrhythmia, septic shock, liver dysfunction, acute kidney injury, and multi-organ failure.

COVID toe:

	

Some patients have reported a rash, and others have developed hives, but increasing numbers of patients in the United States and Europe have

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developed painful red inflammation of the toes, similar to the chilblains found with cold exposure. Most patients have been children and young adults, those who are otherwise healthy.

The toes may become edematous and appear red at first and then purple. Some may develop petechial macular lesions. The lesions may appear on a few toes or all toes on both feet. The lesions may be easily overlooked on dark-skinned patients but swelling and slight discoloration of the skin may be evident.

There are also reports of patients with finger lesions. Although the lesions are painful and may itch or burn, generally the lesions resolve with no problem over time although some have required amputation. Some people report that they take diphenhydramine to relive the itching.

Cardiac injury: Studies indicate that about 20% of patients with COVID-19 have indications of heart injury, even if they don't have respiratory symptoms. It appears that COVID causes generalized inflammation, referred to as a cytokine storm, that can affect many organs, including the heart. Additionally, some of the drugs that have been studied, such as hydrochloroquine and remdesivir, may cause cardiac damage. Patients may develop myocarditis and heart failure. The virus may also directly infect cardiovascular muscles.

A cardiologist interviewed on CNN reported that patients who now have or have had COVID-19 infection are presenting with symptoms that mimic those of a heart attack (chest pain, pressure, shortness of breath) and that ECG changes are similar. The physician suggested that all patients presenting with signs of a heart attack should be checked for COVID-19.

Kidney failure: Studies show that up to 30% of patients hospitalized for COVID-19 in New York and China and other places as well have shown signs of kidney failure with some requiring dialysis, posing a problem for hospitals lacking adequate dialysis equipment and staff training. It's unclear exactly what mechanism is involved in damage to the kidneys, but it could be from direct infection, hypoxemia, cytokine storm, or blood clots.

It's still not clear whether patients will regain kidney function if they recover from COVID-19 infection.

Blood clots: Patients with COVID-19 are at greater risk of developing blood clots, often multiple, than other hospitalized or bedridden patients, with studies in Europe indicating that 20% to 30% of critically ill patients develop clots. Even young people are developing and sometimes dying from COVID-

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associated strokes, and anticoagulants have not been reliably effective in preventing clots.

Patients with high levels of D-dimer have a high risk of mortality from blood clots. Autopsies have shown that capillaries in some patients were clogged with small clots. This may be the reason that some patients exhibit very low levels of oxygen and do not respond to mechanical ventilation. The reason for the formation of blood clots is not yet clear, but it may be related to the cytokine storm that can occur with COVID-19.

Long COVID: While most patients with COVID-19 recover within a few weeks, some have symptoms that persist for many weeks or months or possibly even longer. Common persistent symptoms may include dyspnea, fatigue, joint pain, chest pain, myopathy, headaches, tachycardia, loss of smell or taste, depression anxiety, fever, dizziness and "brain fog."

Those who are most at risk include those who are older with serious medical conditions, but it has also occurred in young people. Organs affected may include:

- Heart: Damage to the heart muscle and increased risk of heart failure.
- Lungs: Permanent damage to alveoli. Some patients have required lung transplants.
- Brain: Seizures, strokes, Guillain-Barré syndrome.

Other long-term effects that have not yet been identified may occur as time passes.

Multisystem inflammatory syndrome in children (MIS-C) and adults (MIS-A): While children were believed to suffer only mild disease initially, there have been scattered cases of children who became seriously ill, primarily with pneumonia. Recently, however, it has become clear that not only infants and children but also adolescents and young adults can develop a syndrome now referred to as multisystem inflammatory syndrome in children (MIS-C). Similar symptoms can also occur in adults (MIS-A).

Symptoms are similar to those of Kawasaki disease (which typically only affects Asian children under 5 years) and toxic shock syndrome. Symptoms common to both children and adults include fever AND any of the following signs and symptoms:

- Abdominal (gut) pain
- Bloodshot eyes
- Chest tightness/pain
- Diarrhea
- Feeling extra tired

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- Headache
- Low blood pressure
- Neck pain
- Rash
- Vomiting

Different organs may become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, and GI organs. Symptoms are similar in adults and children, but this MIS is more common in children than adults.

Criteria for diagnosis (CDC) of MIS-C include:
- Age <21 with fever, laboratory evidence of inflammation, and evidence of severe illness with multisystem organ involvement requiring hospitalization AND
- No alternative plausible diagnosis AND
- Positive findings of current or recent COVID-19 infection or positive antigen test or COVID-19 exposure within preceding 4 weeks.

Criteria for diagnosis of MIS-A include:
- Age 21 or older.
- Fever ≥38º C for ≥24 hours before hospitalization or within 3 days of hospitalization AND at least 3 of the following with at least 1 being primary:
    - Primary clinical criteria: Severe cardiac illness and rash AND non-purulent conjunctivitis.
    - Secondary clinical criteria: New onset neurologic signs and symptoms; shock or hypotension (not attributed to therapy); abdominal pain, vomiting, or diarrhea; and thrombocytopenia (<150,000).
- Laboratory evidence: Elevated levels of at least 2 of the following: C-reactive protein, ferritin, IL-6, ESR, procalcitonin AND positive SARS-CoV-2 test.

The children affected by MIS-C have been infected with COVID-19 or have antibodies, suggesting an earlier infection that in many cases was asymptomatic. As of August 20, 2020, 694 confirmed cases, resulting in 11 deaths had occurred in the United States with cases reported in 42 states and Washington, DC. By July 30, 2021, 4404 cases of MIS-C had been confirmed with 37 deaths. Most cases have been in ages 1 though 14 although the range is 1 to 20.

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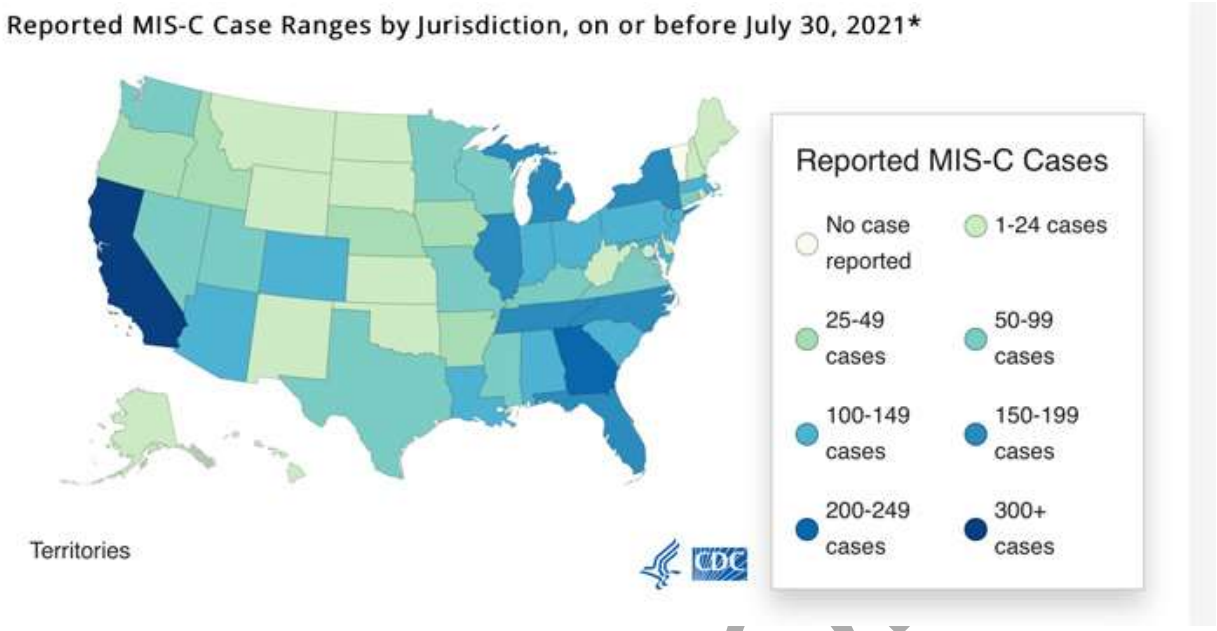

The true numbers of this complication are not yet clear as it has been so recently identified. Cases have been reported in other countries, including the UK, Italy, and Spain. Symptoms typically develop 2 to 4 weeks after infection with COVID-19.

Children and young adults with MIS-C are treated as for Kawasaki disease with IV immunoglobulin, corticosteroids, aspirin, and supportive care, depending on the severity of symptoms.

Risk factors for progression to severe disease with COVID-19

According to the NIH, these are risk factors that may result in progression to severe disease with COVID-19:

- An immunocompromising condition or immunosuppressive treatment. Many experts strongly recommend therapy for patients with these conditions, despite their limited representation in clinical trials.
- Being overweight (BMI 25–30) as the sole risk factor.
- Chronic kidney disease.
- Pregnancy.
- Sickle cell disease.
- Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies).
- Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation that is not related to COVID-19).

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Diagnosis of COVID-19

Testing is guided by the CDC, which initially recommended multiple specimens from upper and lower respiratory tract for PCR assay and serologic testing. Tests were originally available only from the CDC but many medical facilities, states, and companies have now developed testing so opportunities for testing have expanded. A point-of-care test that requires only 5 to 15 minutes to results has been developed and is available commercially but has about a 15% error rate.

Summary Recommendations

- To diagnose acute infection of SARS-CoV-2, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using a nucleic acid amplification test (NAAT) with a sample collected from the upper respiratory tract (i.e., a nasopharyngeal, nasal, or oropharyngeal specimen) **(AIII)**.
- For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:
  - The Panel recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative **(BII)**.
  - The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 **(BII)**.
- A NAAT should not be repeated in an asymptomatic person within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2 **(AIII)**.
- SARS-CoV-2 reinfection has been reported in people who have received an initial diagnosis of infection; therefore, a NAAT should be considered for persons who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis **(BIII)**.
- The Panel **recommends against** the use of serologic (i.e., antibody) testing as the sole basis for diagnosis of acute SARS-CoV-2 infection **(AIII)**.
- The Panel **recommends against** the use of serologic (i.e., antibody) testing to determine whether a person is immune to SARS-CoV-2 infection **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

NIH

Multiple other tests and imaging may be ordered depending on the patient's symptoms.

Transmission and prevention

COVID-19 appears to spread both through droplets and airborne transmission and is more contagious than the flu. The reproduction number or R0 (pronounced R-nought) is the number of people that one infected person will in turn infect. The R0 for flu is 1.3, for measles 12 to 18, and a current estimate is that the R0 of COVID-19 ranges from 1.4 to 3.9.

COVID-19 infects the body by attaching to angiotensin converting enzyme 2 (ACE 2) receptors, which are expressed by epithelial cells in the nares, oral cavity, lungs, intestines, heart, kidneys, and blood vessels, which can account for the variety of different symptoms that patients exhibit.

There is clear evidence that COVID-19 is airborne, and cases are generally treated accordingly in healthcare facilities, with patients placed in negative pressure rooms as long as they are available although appropriate PPE and infection control procedures were often not available in the early months. Studies have shown that the coronavirus may remain in the air for up to 3 hours. A recent study suggests that the virus can travel up to 19 feet if the person coughs and up to 26 feet with a sneeze.

The infection is contagious even in those who are asymptomatic, and patients may remain infectious even after symptoms subside. This is a distinct difference from SARS and MERS and increases the risk of transmission. Recent studies suggest that about 40% of those who are infected are asymptomatic. However, it has been reported that even asymptomatic patients may show changes on chest x-rays, suggesting that asymptomatic infections may not be as benign as some believe.

Additionally, studies indicate that those who are fully vaccinated can spread the disease, especially now that the delta virus predominates, and can become infected and ill although the severity of the disease is usually less and the death rate from those who are fully vaccinated remains very low. Currently, COVID-19 infections and deaths are occurring primarily in those who are unvaccinated

Close contact is generally defined for this coronavirus as within 6 feet or within the room or care area for a prolonged period without appropriate PPE, including N95 respirator. Healthcare providers and those in close contact with infected patients should adhere to standard, contact, and airborne precautions.

A study by the CDC found that COVID-19 survived on the *Diamond Princess* cruise ship for up to 17 days, but researchers are unsure if transmission occurred as the result of surface contamination.

Because most people (but not all) exhibit fever, checking temperatures is one of the main tools used now to identify people who may be infected. The CDC recommends that those who have been exposed check their temperatures twice daily and contact a physician if the temperature exceeds 100.4° F.

In the United States, the federal government was slow in making recommendations and left it to the states to issue mandatory guidelines, which have included:

- Stay at home.

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- Home school
- Avoid gatherings of more than 10 people.
- Close restaurants, bars, food courts, gyms, and other venues.
- Avoid travel.
- Stay away from others if underlying health condition or sickness.
- Practice good hygiene and frequent handwashing

Most states issued some form of stay-at-home order, but not all. In some cases, restrictions applied to only part of a state. Most states closed restaurants and bars except for take-out and delivery, but restaurants and bars remained open in in some states and have generally reopened across the country. Cities tend to have more restrictions that rural areas

Initially, the WHO and CDC did not recommend that the public use face masks although China and South Korea stressed the importance of face masks in reducing transmission. In the United States, the recommendations regarding masks have been confusing at best. First, people were advised not to wear masks, then they were advised to wear masks, then they were advised to wear masks if unvaccinated.

Now, however, it is again recommended that everyone except children under 2 years wear facemasks in public indoor spaces in areas of high transmission (most areas of the United States) and maintain a social distance of at least 6 feet, stressing that the masks prevent others from becoming infected although there is some protection from the wearer as well. This suggests that the primary reason that masks were not recommended initially is that the supply was too low rather than that they were not helpful. One study reported that face masks cut transmission by 50%. N95 masks, which are more effective, have been in short supply even in hospitals.

In an ideal world, healthcare providers would be outfitted in hazmat suits and N95 masks, but at the moment, this is not an ideal world. Most guidelines regarding the use of face masks in hospitals during the height of the pandemic were loosened by the CDC to allow reuse of masks and the CDC even suggested use of a bandana tied about the face if no masks were available. Healthcare workers have become infected and many have died.

Treatment

As with SARS and MERS, treatment initially was primarily supportive because no specific treatment had been found to be effective. In response to demands for treatment approval, on March 29, 2020, the FDA approved the use of chloroquine and hydroxychloroquine (anti-malarial drugs) for

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teenagers and adults if no clinical trial was available although the evidence for use was primarily anecdotal and slim at best.

A study in China found that hydroxychloroquine was no more effective than standard supportive treatment. However, a study in France with only with 20 patients was more positive. Fourteen patients received hydroxychloroquine alone and half got better. However, the small sample size precluded making a conclusive determination of effectiveness.

Despite the weakness of evidence and adverse effects (including cardiac damage) associated with the drug, hydrochloroquine was touted by President Trump (who later claimed he was taking it for preventive purposes), leading to as rush to prescribe the drug. Subsequent research indicated that hydrochloroquine did not shorten the course of the disease, and those treated with the drug had a higher rate of mortality.

Remdesivir, another drug, has been shown to shorten the course of the disease, and other drugs are now in use, but the mortality rate of severely ill patients remains high. Clinical trials are still evaluating the efficacy of many different drugs.

About 20 to 30% of those hospitalized for pneumonia require intensive care treatment. Treatment may include high flow oxygen, intubation and ventilation, and $ECMO_2$. Many patients require dialysis. Patients are often positioned on their abdomens for at least part of each day in order to facilitate expansion of their lungs.

Supportive treatments include:

- Acetaminophen, ibuprofen for fever and discomfort.
- Albuterol for shortness of breath.
- Oxygen to relieve shortness of breath.
- Prone positioning to improve lung expansion.
- Adequate fluids.

The NIH has issued a series of recommendations for treatment of patients with COVID-19.

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Recommendations for nonhospitalized patients with acute COVID-19 not requiring oxygen
• Supportive care and isolation • Initial triage by telehealth but those with dyspnea should have in-person evaluation.
Those at high risk of disease progression: • Casirivimab plus imdevimab OR • Sotrovimab
DO NOT USE: • Bamlanivimab plus etesevimab (new variants may be resistive) • Systemic glucocorticoids (such as dexamethasone) unless other indications are present.

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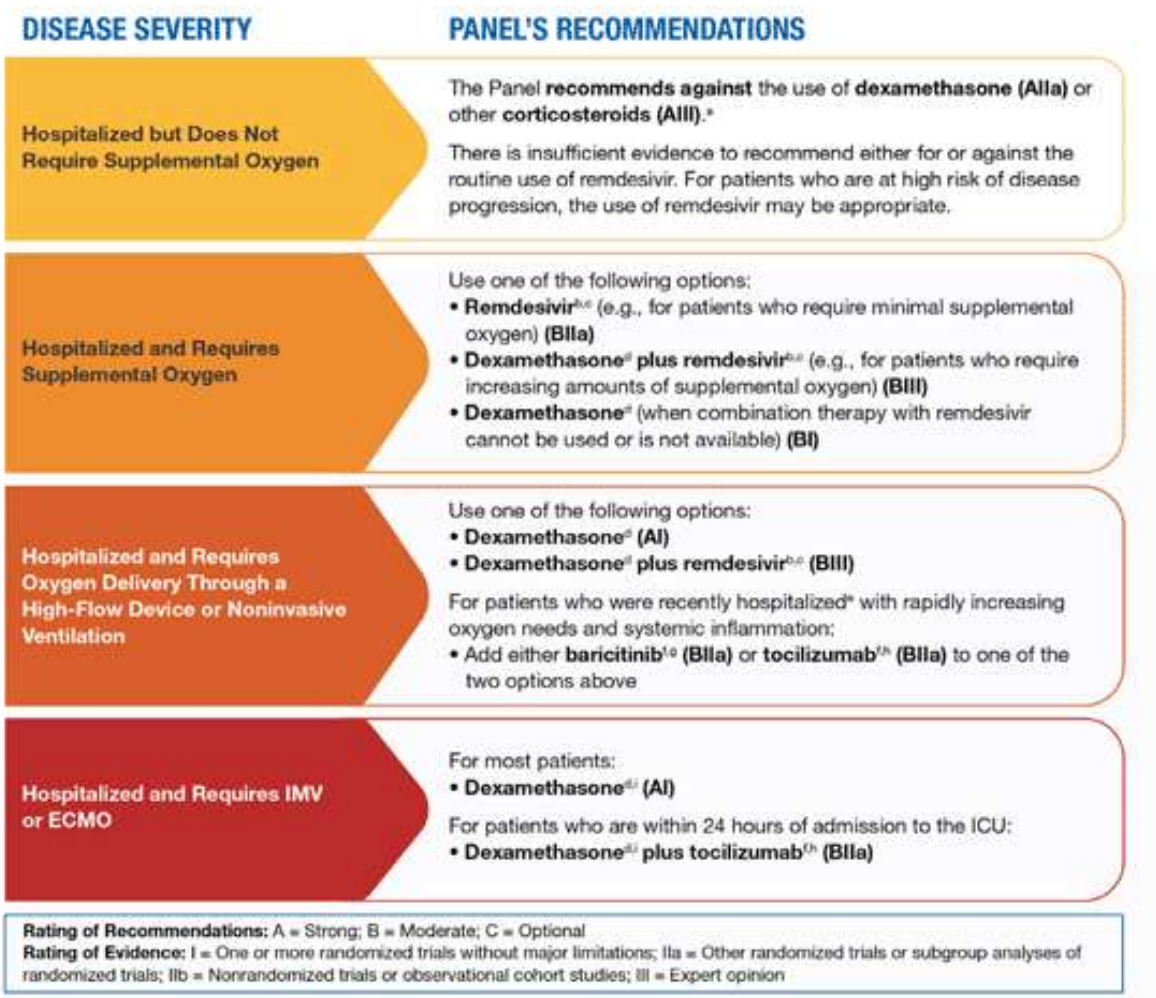
Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity



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Numerous clinical trials have been carried out with monoclonal antibodies, which may block the COVID-19 coronavirus from attaching to host cells and replicating and may also neutralize the coronavirus, and the FDA has issued emergency use authorizations (EUA) (which is different from FDA approval but based on review of scientific evidence and need) for a number of drugs.

Monoclonal antibodies are laboratory-produced proteins that provide an immune response to help fight harmful antigens, such as the coronavirus. Studies remain ongoing. For example, an EUA was issued for Banlanivimab in November 2020, but the drug is no longer recommended for use because new variants may be resistive.

The FDA recently issued an emergency use authorization for another antibody treatment (REGEN-COV) for those 12 and older who have been exposed to COVID-19 and are at high risk in order to prevent severe infection.

While trials have been carried out using convalescent plasma, this is no longer recommended. Convalescent plasma is plasma that contains antibodies to COVID-19 and is derived from patients who have recovered from COVID-19 infections. Prior to the development of vaccines, it was believed that the antibodies might help to treat the disease and prevent progression to severe disease. More than 100,000 people received convalescent plasma as part of clinical trials.

However, in February 2021, the NIH halted trials with COVID-19 convalescent plasma for mild to moderate symptoms because it was found that, while it caused no harm, it did not improve outcomes.

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Summary Recommendations

Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibodies, listed in alphabetical order, to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization (EUA) criteria:
  - **Casirivimab plus imdevimab**; *or*
  - **Sotrovimab**
- When using casirivimab plus imdevimab, the Panel recommends:
  - **Casirivimab 600 mg plus imdevimab 600 mg IV infusion (AIIa)**
  - If IV infusions are not feasible or would cause a delay in treatment, **casirivimab 600 mg plus imdevimab 600 mg** administered by four subcutaneous injections (2.5 mL per injection) can be used as an alternative **(BIII)**.
- At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab** for the treatment of COVID-19 **(AIII)** because the Gamma (P.1) and Beta (B.1.351) variants of concern, which have reduced susceptibility to both agents, are circulating in the United States. See the Centers for Disease Control and Prevention COVID Data Tracker for the latest information on variant proportions by region in the United States.
- The strength of the evidence for using anti-SARS-CoV-2 monoclonal antibodies for the treatment of COVID-19 varies depending on the factors that place patients at risk for progression to severe COVID-19 and/or hospitalization (see Anti-SARS-CoV-2 Monoclonal Antibodies for details). The recommendations are based on the following criteria from the Food and Drug Administration EUAs:
  - Patients with high-risk conditions that were represented in clinical trials **(AIIa)**, *and*
  - Patients with other medical conditions and factors that had limited representation in clinical trials **(BIII)**; however, for patients who have an immunocompromising condition or who are receiving immunosuppressive therapy, the rating is **AIII**.
- Treatment with anti-SARS-CoV-2 monoclonal antibodies should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- The use of anti-SARS-CoV-2 monoclonal antibodies should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet EUA criteria for outpatient treatment.
- Anti-SARS-CoV-2 monoclonal antibodies are not currently authorized for use in patients who are hospitalized with severe COVID-19; however, they may be available through expanded access programs for patients who have not developed an antibody response or who are not expected to mount an effective immune response to SARS-CoV-2 infection.

COVID-19 Convalescent Plasma

- The Panel **recommends against** the use of **low-titer COVID-19 convalescent plasma** for the treatment of COVID-19 **(AIIb)**. Low-titer COVID-19 convalescent plasma is no longer authorized through the convalescent plasma EUA.
- For hospitalized patients with COVID-19 who do not have impaired immunity:
  - The Panel **recommends against** the use of **COVID-19 convalescent plasma** for the treatment of COVID-19 in mechanically ventilated patients **(AI)**.
  - The Panel **recommends against** the use of **high-titer COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients who do not require mechanical ventilation, except in a clinical trial **(AI)**.
- For hospitalized patients with COVID-19 who have impaired immunity:
  - There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.

Summary Recommendations, continued
• For nonhospitalized patients with COVID-19:   • There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19. **Anti-SARS-CoV-2 Specific Immunoglobulin** • There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 specific immunoglobulins for the treatment of COVID-19.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

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Recommendations for patient discharged from inpatient setting
Stable condition not requiring oxygen: • DO NOT continue remdesivir, dexamethasone, or baricitinib.
Stable but requiring oxygen: • Consider use of remdesivir, dexamethasone, or baricitinib.
Patient discharged with new or increasing need for supplemental oxygen: • Dexamethasone 6 mg PO daily while on supplemental oxygen (but not to exceed 10 days). • Consider use of remdesivir. • DO NOT use baricitinib except for clinical trials.

Mortality rate

The reported mortality rate varies widely, ranging from <1% to over 8%, and the reason for this is not clear but may reflect widespread testing identifying more asymptomatic cases in some countries, the age of the patients, smoking rates, or other variables. China originally reported a fatality rate of 2.3%. The actual mortality rate is very difficult to determine at this time because much early testing was only of symptomatic and/or hospitalized patients and excluded those who were infected but asymptomatic. Many deaths that were actually caused by COVID may have been attributed to other causes.

While China and Europe (primarily the UK, Italy, France, and Spain) were originally ahead of the United States in cases and mortality rates, the United States now has the most cases and most deaths of any country in the world even though cases decreased for a period of time. Currently (August 2021), Mexico has a mortality rate of 8.2% and the United States of 1.7%, likely because patients in the United States have better access to effective treatment.

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Conclusion

For years, public health officials have warned that another pandemic could sweep the world and result in millions of deaths, such as the 1919 Spanish flu that killed about 50 million people and HIV/AIDS that killed 25 million. While antibiotic resistant bacteria certainly are a concern, viruses have posed the greatest threats, including Ebola virus outbreaks in Africa and the coronavirus outbreaks in China and the Middle East.

It is increasingly difficult to confine an outbreak to a small area because of international travel and commerce. When one outbreak, such as SARS, subsides, another one appears, such as MERS and the more recent coronavirus—COVID-19. COVID-19 has become a pandemic that has killed millions of people throughout the world and continues to pose a serious health threat.

As long as the coronavirus continues to be transmitted, there is a risk of more and even deadlier mutations, and the infections are likely to continue to spread until 80% to 90% of the population is vaccinated—but this target seems increasingly difficult to reach.

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