Overview of COVID-19: Epidemiology, Clinical Presentation, and Transmission

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Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of July 9, 2020, more than 12 million cases of COVID-19—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—have been reported globally, including more than 550,000 deaths. Cases have been reported in more than 180 countries, including all 50 states of the United States.1,2

Individuals of all ages are at risk for infection and severe disease. However, the probability of serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions. In a recent analysis of more than 1.3 million laboratory-confirmed cases that were reported in the United States between January and May 2020, 14% of patients required hospitalization, 2% were admitted to the intensive care unit, and 5% died.3 The percentage of patients who died was 12 times higher (19.5% vs. 1.6%) and the percentage of patients who were hospitalized was six times higher (45.4% vs. 7.6%) in those with reported medical conditions than in those without medical conditions. The mortality rate was highest in those aged >70 years, regardless of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, obesity, sickle cell disease, transplant recipients, and other immunocompromising conditions.2,4-9

Emerging data from the United States suggest that racial and ethnic minorities experience higher rates of COVID-19 and subsequent hospitalization and death.10-14 However, surveillance data that include race and ethnicity are not available for most reported cases of COVID-19 in the United States.2,15 Factors that contribute to the increased burden of COVID-19 in these populations may include over-representation in work environments that confer higher risks of exposure to COVID-19, economic inequality (which limits a person’s ability to protect against COVID-19 exposure), neighborhood disadvantage,16 and a lack of access to health care.15 Structural inequalities in society contribute to health disparities for racial and ethnic minority groups, including higher rates of comorbid conditions (e.g., cardiac disease, diabetes, hypertension, obesity, pulmonary diseases), which further increases the risk for severe illness from COVID-19.14

Clinical Presentation

The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days.6,17,18 The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and death. Among 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency ≥30 breaths/min, \(\text{SpO}_2\) ≤93%, \(\text{PaO}_2/\text{FiO}_2\) <300 mmHg, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure).19 In a report on more than 370,000 confirmed COVID-19 cases with reported symptoms in the United States, 70% of patients experienced fever, cough, or shortness of breath, 36% had muscle aches, and 34% reported headaches.3 Other reported symptoms have included, but are not limited to, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.

The abnormalities seen in chest X-rays vary, but bilateral multi-focal opacities are the most common. The abnormalities seen in computed tomography (CT) of the chest also vary, but the most common are bilateral peripheral ground-glass opacities, with areas of consolidation developing later in the clinical course.20 Imaging may be normal early in infection and can be abnormal in the absence of symptoms.20

Common laboratory findings of COVID-19 include leukopenia and lymphopenia. Other laboratory abnormalities have included elevated levels of aminotransferase, C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase.
While COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac, dermatologic, hematological, hepatic, neurological, renal, and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk in critically ill patients. The long-term sequelae of COVID-19 survivors are currently unknown.

Recently, SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children or MIS-C). Please see Special Considerations in Children for more information.

### Routes of SARS-CoV-2 Transmission

Transmission of SARS-CoV-2 occurs primarily through respiratory secretions, and, to a lesser extent, contact with contaminated surfaces. Most transmissions are thought to occur through droplets; covering coughs and sneezes and maintaining a distance of six feet from others can reduce the risk of transmission. When consistent distancing is not possible, face coverings may further reduce the spread of droplets from infectious individuals to others. Frequent handwashing is also effective in reducing acquisition.

The onset and duration of viral shedding and the period of infectiousness are not completely defined. Viral RNA may be detected in upper respiratory specimens from asymptomatic or pre-symptomatic individuals with SARS-CoV-2. An increasing number of studies have described cases where asymptomatic individuals have transmitted SARS-CoV-2. The extent to which this occurs remains unknown, but this type of transmission may be contributing to a substantial amount of community transmission.

### References


Testing for SARS-CoV-2 Infection

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Virologic Testing for SARS-CoV-2 Infection

Virologic testing (i.e., using a molecular diagnostic or antigen test to detect SARS-CoV-2) should be done in all persons with a syndrome consistent with COVID-19 and in people with known high-risk exposures to SARS-CoV-2. Ideally, virologic testing should also be performed in people likely to be at repeated risk of exposure, such as health care workers and first responders. For more information, see the Centers for Disease Control and Prevention (CDC) COVID-19 website.

While initial diagnostic tests for SARS-CoV-2 infection have relied on reverse transcriptase polymerase chain reaction platforms, more recent tests have included a variety of additional platforms. A number of diagnostic tests for SARS-CoV-2 infection have received emergency use authorizations (EUAs) issued by the Food and Drug Administration (FDA). Formal comparisons of the sensitivity and specificity of these tests are in progress.

The CDC recommends that nasopharynx samples be used to detect SARS-CoV-2. Nasal swabs or oropharyngeal swabs are acceptable alternatives. Although lower respiratory tract samples have a higher yield than upper tract samples, they are often not obtained because of concerns about aerosolization of virus during sample collection procedures.

The CDC has established a priority system for diagnostic testing for SARS-CoV-2 infection based on the availability of tests; the CDC testing guidance is updated periodically.

The following are the current CDC priorities for COVID-19 diagnostic testing:

**High Priority:**
- Hospitalized patients with symptoms
- Health care facility workers, workers in congregate living settings, and first responders with symptoms
- Residents in long-term care facilities or other congregate living settings, including prisons and shelters, with symptoms.

**Priority:**
- Persons with symptoms of potential COVID-19 infection, including fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhea, and/or sore throat
- Persons without symptoms who are prioritized by health departments or clinicians, for any reason, including but not limited to public health monitoring, sentinel surveillance, or screening of
Molecular diagnostic and antigen tests can yield false-negative results. In people with a high likelihood of infection based on exposure history and/or clinical presentation, a single negative test result does not completely exclude SARS-CoV-2 infection, and repeat testing should be considered. When a person who is strongly suspected to have SARS-CoV-2 infection has a negative result on an initial antigen test, repeat testing using a molecular diagnostic test may be warranted.

**Serologic (or Antibody) Testing for Diagnosis of SARS-CoV-2 Infection**

Unlike molecular diagnostic and antigen tests for SARS-CoV-2 that detect the presence of the virus, serologic tests are intended to identify persons with recent or prior SARS-CoV-2 infection. Because it may take 21 days or longer after symptom onset for seroconversion or detection of immunoglobulin M and/or immunoglobulin G antibodies to SARS-CoV-2, the Panel does not recommend the use of serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection (AIII). Given that molecular diagnostic tests and antigen tests for SARS-CoV-2 occasionally yield false-negative results, in some settings, serologic tests have been used as an additional diagnostic test in patients strongly suspected to have SARS-CoV-2 infection.

No serologic tests for SARS-CoV-2 are approved by the FDA and some, but not all, commercially available serologic tests for SARS-CoV-2 have received EUAs issued by the FDA. Several professional societies and federal agencies, including the Infectious Diseases Society of America, CDC, and FDA, provide guidance for clinicians regarding serologic testing for SARS-CoV-2.

Several factors should be considered when using these tests, including:

- Important performance characteristics, including the sensitivity and specificity (i.e., the rate of true positive and true negative results) of many of the commercially available serologic tests, have not been fully characterized. Serologic assays that have FDA EUAs are preferred for public health and clinical use. Formal comparisons of serologic tests are in progress.
- False-positive test results may occur due to cross-reactivity from pre-existing antibodies to other coronaviruses.

**Serologic Testing and Immunity to SARS-CoV-2 Infection**

The Panel recommends against the use of serologic testing to determine whether a person is immune to SARS-CoV-2 infection (AIII). If serologic tests are performed and antibody is detected, results should be interpreted with caution for the following reasons:

- It is currently unknown how long antibodies persist following infection, and
- It is currently unknown whether the presence of antibody confers protective immunity against future infection.

In communities where the prevalence of SARS-CoV-2 infection is low, the proportion of positive tests that are false positives may be quite high. In these situations, confirmatory testing using a second independent antibody assay, ideally one that uses a different antigenic target (e.g., the nucleocapsid phosphoprotein if the first assay targeted the spike glycoprotein), can substantially improve the probability that persons with a positive test result are antibody positive.

Assuming the test is reliable, serologic tests to identify recent or prior SARS-CoV-2 infection may be used to:
• Determine who may be eligible to donate blood to manufacture convalescent plasma.
• Measure the immune response in SARS-CoV-2 vaccine studies.
• Estimate the proportion of the population exposed to SARS-CoV-2.

Lastly, serologic tests should not be used to:

• Make decisions about the grouping of persons residing in or being admitted to congregate settings (e.g., schools, dormitories, correctional facilities), or
• Determine whether persons should return to the workplace.

References


Prevention and Prophylaxis of SARS-CoV-2 Infection

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**Summary Recommendations**

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any agents for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pre-exposure prophylaxis (PrEP), except in a clinical trial (AIII).
- The Panel **recommends against** the use of any agents for SARS-CoV-2 post-exposure prophylaxis (PEP), except in a clinical trial (AIII).

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

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

**General Prevention Measures**

Most transmissions of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are thought to occur through respiratory droplets, and the risk of transmission can be reduced by covering coughs and sneezes and maintaining a distance of at least 6 feet from others. When consistent distancing is not possible, face coverings may further reduce the spread of droplets from infectious individuals to others. Frequent handwashing is also effective in reducing the risk of acquisition.¹ Health care providers should follow the Centers for Disease Control and Prevention (CDC) recommendations for infection control and appropriate use of personal protective equipment.²

**Vaccines**

Vaccines for SARS-CoV-2 are aggressively being pursued. Vaccine development is typically a lengthy process, often requiring multiple candidates before one proves to be safe and effective. To address the current pandemic, several platforms are being used to develop candidate vaccines for Phase 1/2 trials; those that show promise are rapidly moving into Phase 3 trials. Several standard platforms, such as inactivated vaccines, live-attenuated vaccines, and protein subunit vaccines, are being pursued. Some novel approaches are being investigated, including DNA-based and RNA-based strategies and replicating and nonreplicating vector strategies, with the hope of identifying a safe and effective vaccine that can be used in the near future.³⁴

**Pre-Exposure Prophylaxis**

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any agents for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial (AIII).

**Rationale**

At present, no known agent that is administered before exposure (i.e., as PrEP) can prevent SARS-CoV-2 infection. Clinical trials are investigating several agents, including emtricitabine plus tenofovir alafenamide or tenofovir disoproxil fumarate, hydroxychloroquine, and supplements such as zinc, vitamin C, and vitamin D. Studies of monoclonal antibodies that target SARS-CoV-2 are in development. Please check ClinicalTrials.gov for the latest information.

**Post-Exposure Prophylaxis**

- The Panel **recommends against** the use of any agents for SARS-CoV-2 post-exposure prophylaxis (PEP), except in a clinical trial (AIII).
**Rationale**

At present, no known agent can prevent SARS-CoV-2 infection after exposure (i.e., as PEP). Potential options for PEP that are currently under investigation include chloroquine, hydroxychloroquine, lopinavir/ritonavir, nitazoxanide, vitamin super B-complex, and vitamin D. Other strategies that are in development include the use of SARS-CoV-2 monoclonal antibodies and convalescent plasma. Please check ClinicalTrials.gov for the latest information.

**Clinical Trial Data**

Both chloroquine and hydroxychloroquine have *in vitro* activity against SARS-CoV and SARS-CoV-2.\(^5,6\)

A small cohort study without a control group has suggested that hydroxychloroquine might reduce the risk of household transmission.\(^7\)

A randomized, double-blind, controlled trial enrolled 821 participants using an internet-based survey. Study participants had either high or moderate risk of occupational exposures (66% of participants) or household exposures (34% of participants). High-risk exposure was defined as being within 6 feet of an individual with confirmed SARS-CoV-2 infection for more than 10 minutes while not wearing a face mask or eye shield (87.6% of participants), and moderate-risk exposure was defined as the same exposure while wearing a face mask but no eye shield (12.4% of participants).\(^8\)

Participants were randomized to receive placebo or hydroxychloroquine sulfate given once at a relatively high dose of 800 mg, followed by 600 mg 6 to 8 hours later, then 600 mg once daily for 4 additional days. Because enrollment was done online, study drugs were sent by overnight mail, resulting in more than 50% of participants initiating their first dose 3 to 4 days after exposure to SARS-CoV-2.\(^8\)

A total of 107 participants had a primary outcome of symptomatic illness, with SARS-CoV-2 infection confirmed by molecular test or by the development of a compatible, COVID-19-related syndrome based on CDC criteria. Due to limited access to molecular diagnostic testing, confirmation of infection occurred for only 16 of the 107 participants (15%). There was no statistically significant difference between the incidences of a primary outcome in the hydroxychloroquine and placebo groups (11.8% vs. 14.3%, respectively; \(P = 0.35\)). There were more adverse events in the hydroxychloroquine group; mostly nausea, loose stools, and abdominal discomfort, with no serious adverse reactions or cardiac arrhythmias.\(^8\)

This study had several important limitations, including:

- Initiation of therapy was delayed for at least 3 days after exposure to SARS-CoV-2 in the majority of participants.
- Only 15% of participants who reached the primary outcome had SARS-CoV-2 infection confirmed by molecular diagnostics.
- The study population was young (with a median age of 40 years) and consisted of participants who had a relatively low risk of severe COVID-19.

It is notable that while high doses of hydroxychloroquine were associated with an increase in the frequency of adverse events, the reported adverse events were mostly mild, with no serious events reported.

**References**


Management of Persons with COVID-19

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Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can experience a range of clinical manifestations, from no symptoms to critical illness. This section of the Guidelines discusses the clinical management of patients according to illness severity. Currently, the Food and Drug Administration has not approved any drugs for the treatment of COVID-19. However, an array of drugs approved for other indications, as well as multiple investigational agents, are being studied for the treatment of COVID-19 in several hundred clinical trials around the globe. Some drugs can be accessed through Emergency Use Authorization, expanded access programs, or compassionate use mechanisms. Available clinical data for these drugs under investigation are discussed in Antiviral Therapy and Immune-Based Therapy.

In general, adults with COVID-19 can be grouped into the following severity of illness categories, although the criteria in each category may overlap or vary across guidelines and clinical trials:

- **Asymptomatic or Presymptomatic Infection**: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.
- **Mild Illness**: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.
- **Moderate Illness**: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen ($SpO_2$) $\geq 94\%$ on room air at sea level.
- **Severe Illness**: Individuals who have respiratory frequency $>30$ breaths per minute, $SpO_2 < 94\%$ on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($PaO_2/FiO_2$) $< 300$ mmHg, or lung infiltrates $>50\%$.
- **Critical Illness**: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

In pediatric patients, radiographic abnormalities are common and, for the most part, should not be used as the sole criteria to define COVID-19 illness category. Normal values for respiratory rate also vary with age in children, thus hypoxia should be the primary criteria to define severe illness, especially in younger children.

**Asymptomatic or Presymptomatic Infection**

Asymptomatic SARS-CoV-2 infection can occur, although the percentage of patients who remain truly asymptomatic throughout the course of infection is variable and incompletely defined. It is unclear at present what percentage of individuals who present with asymptomatic infection may progress to clinical disease. Some asymptomatic individuals have been reported to have objective radiographic findings consistent with COVID-19 pneumonia. Over time, the availability of widespread virologic testing for SARS-CoV-2 and the development of reliable serologic assays for antibodies to the virus will help determine the true prevalence of asymptomatic and presymptomatic infections.¹

Persons who test positive for SARS-CoV-2 by molecular diagnostic or antigen testing (see Testing for SARS-CoV-2) and who are asymptomatic should self-isolate at home. If they remain asymptomatic, they can discontinue isolation 10 days after the date of their first positive SARS-CoV-2 test.² Health care workers who test SARS-CoV-2 positive and are asymptomatic may obtain additional guidance.
from their occupational health service. See the Centers for Disease Control and Prevention COVID-19 website for detailed information. Individuals who become symptomatic should contact their health care provider for further guidance. Current CDC recommendations for individuals who develop symptoms are to self-isolate for at least 10 days from the onset of their symptoms and until they have no fever and improvement in respiratory symptoms for at least 3 days.

**The Panel recommends no additional laboratory testing and no specific treatment for persons with suspected or confirmed asymptomatic or presymptomatic SARS-CoV-2 infection (AIII).**

**Mild Illness**

Patients may have mild illness defined by a variety of signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea on exertion, or abnormal imaging. Most mildly ill patients can be managed in an ambulatory setting or at home through telemedicine or remote visits.

All patients with symptomatic COVID-19 and risk factors for severe disease should be closely monitored. In some patients, the clinical course may rapidly progress.3,4

No specific laboratory evaluations are indicated in otherwise healthy patients with mild COVID-19 disease.

**There are insufficient data to recommend either for or against any antiviral or immune-based therapy in patients with COVID-19 who have mild illness.**

**Moderate Illness**

Moderate COVID-19 illness is defined as evidence of lower respiratory disease by clinical assessment or imaging with \( \text{SpO}_2 \geq 94\% \) on room air at sea level. Given that pulmonary disease can rapidly progress in patients with COVID-19, close monitoring of patients with moderate disease is recommended. If bacterial pneumonia or sepsis is strongly suspected, administer empiric antibiotic treatment for community-acquired pneumonia, re-evaluate daily, and if there is no evidence of bacterial infection, de-escalate or stop antibiotics.

Hospital infection prevention and control measures include use of personal protective equipment for droplet and contact precautions along with eye protection (e.g., masks, face shields/goggles, gloves, gowns) and single-patient dedicated medical equipment (e.g., stethoscopes, blood pressure cuffs, thermometers).5,6 The number of individuals and providers entering the room of a patient with COVID-19 should be limited. If necessary, patients with confirmed COVID-19 may be cohorted in the same room. If available, airborne infection isolation rooms (AIIRs) should be used for patients who will be undergoing any aerosol-generating procedures. During these procedures, all staff should wear fit-tested respirators (N95 respirators) or powered, air-purifying respirators (PAPRs) rather than a surgical mask.7

The optimal pulmonary imaging technique for people with COVID-19 is yet to be defined. Initial evaluation may include chest x-ray, ultrasound, or if indicated, computerized tomography (CT). Electrocardiogram (ECG) should be performed if indicated. Laboratory testing includes a complete blood count (CBC) with differential and a metabolic profile, including liver and renal function tests. Measurements of inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin, while not part of standard care, may have prognostic value.

Clinicians should refer to Antiviral Therapy and Table 2a and Immune-Based Therapy and Table 3a to review the available clinical data regarding investigational drugs being evaluated for treatment of COVID-19.

**COVID-19 Treatment Guidelines**

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**Severe Illness**

Patients with COVID-19 are considered to have severe illness if they have SpO₂ <94% on room air at sea level, respiratory rate >30, PaO₂/FiO₂ <300 mmHg, or lung infiltrates >50%. These patients may experience rapid clinical deterioration and will likely need to undergo aerosol-generating procedures. They should be placed in AIIRs, if available. Administer oxygen therapy immediately using nasal cannula or high-flow oxygen.

If secondary bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate daily, and, if there is no evidence of bacterial infection, de-escalate or stop antibiotics.

Evaluation should include pulmonary imagining (chest x-ray, ultrasound, or, if indicated, CT) and ECG, if indicated. Laboratory evaluation includes a CBC with differential and a metabolic profile, including liver and renal function tests. Measurements of inflammatory markers such as CRP, D-dimer, and ferritin, while not part of standard care, may have prognostic value.

Clinicians should refer to Antiviral Therapy and Table 2a and Immune-Based Therapy and Table 3a to review the available clinical data regarding drugs being evaluated for treatment of COVID-19.

**Critical Illness**

For additional details, see Care of Critically Ill Patients with COVID-19.

Severe cases of COVID-19 may be associated with acute respiratory distress syndrome, septic shock that may represent virus-induced distributive shock, cardiac dysfunction, elevations in multiple inflammatory cytokines that provoke a cytokine storm, and/or exacerbation of underlying comorbidities. In addition to pulmonary disease, patients with COVID-19 may also experience cardiac, hepatic, renal, and central nervous system disease.

Because patients with critical illness are likely to undergo aerosol-generating procedures, they should be placed in AIIRs when available.

Most of the recommendations for the management of critically ill patients with COVID-19 are extrapolated from experience with other life-threatening infections. Currently, there is limited information to suggest that the critical care management of patients with COVID-19 should differ substantially from the management of other critically ill patients, although special precautions to prevent environmental contamination by SARS-CoV-2 is warranted.

The Surviving Sepsis Campaign (SSC), an initiative supported by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, issued Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) in March 2020. The Panel relied heavily on the SSC guidelines in making the recommendations in these Treatment Guidelines and gratefully acknowledges the work of the SSC COVID-19 Guidelines Panel.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 depends on attention to the primary process leading to the ICU admission, but also to other comorbidities and nosocomial complications.

Clinicians should refer to Antiviral Therapy and Table 2a and Immune-Based Therapy and Table 3a to review the available clinical data regarding drugs being evaluated for treatment of COVID-19.

**References**


