3: Overview of COVID-19

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Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of April 19, 2021, more than 141 million cases of COVID-19—caused by SARS-CoV-2 infection—have been reported globally, including more than 3 million deaths.[1]

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 an 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.[2] 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 the presence 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, and other immunocompromising conditions. Transplant recipients and pregnant people are also at a higher risk of severe COVID-19.[3-10]

Emerging data from the United States suggest that racial and ethnic minorities experience higher rates of COVID-19 and subsequent hospitalization and death.[11-15] However, surveillance data that include race and ethnicity are not available for most reported cases of COVID-19 in the United States.[4,16] 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 people's ability to protect themselves against COVID-19 exposure), neighborhood disadvantage,[17] and a lack of access to health care.[16] 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 of developing severe COVID-19.[15]

SARS-CoV-2 Variants of Concern

Like other RNA viruses, SARS-CoV-2 is constantly evolving through random mutations. Any new mutations can potentially increase or decrease infectiousness and virulence. In addition, mutations can increase the virus' ability to evade adaptive immune responses from past SARS-CoV-2 infection or vaccination. This may lead to an increased risk of reinfection or decreased efficacy of vaccines.[18] There is already evidence that some SARS-CoV-2 variants have reduced susceptibility to plasma from people who were previously infected or immunized, as well as to select monoclonal antibodies that are being considered for prevention and treatment.[19]

Since December 2020, several variants of concern have been identified. There is emerging evidence that the B.1.1.7 variant first seen in the United Kingdom is more infectious than earlier variants and may be more virulent.[20-22] It has become the predominant variant in the United Kingdom, and it continues to spread across the globe, including throughout many regions of the United States. The B.1.351 variant that was originally identified in South Africa is now the predominant variant in that region and has spread to many other countries, including the United States. The P.1 variant was originally identified

in Manaus, Brazil, and has now been identified in the United States. Other variants that have emerged in the United States are receiving attention, such as the B.1.427/B.1.429 variants that are circulating throughout California and the B.1.526 variant reported in New York.

The data on the emergence, spread, and clinical relevance of these new variants is rapidly evolving; this is especially true for research on how variants might affect transmission rates, disease progression, vaccine development, and the efficacy of current therapeutics. Because the research on variants of concern is moving quickly, websites such as the Centers for Disease Control and Prevention's National Genomic Surveillance Dashboard and CoVariants.org provide regular updates on the data for SARS-CoV-2 variants. The COVID-19 Treatment Guidelines Panel will review the emerging data on these variants, paying particular attention to research on the impacts of these variants on testing, prevention, and treatment.

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.[6,23,24] The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome 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 $\geq$30 breaths/min, oxygen saturation [SpO_2] $\leq$93%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] <300 mm Hg, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiorgan dysfunction or failure).[25] 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.[2] 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 multifocal opacities are the most common. The abnormalities seen in computed tomography 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 of COVID-19.[26] Imaging may be normal early in infection and can be abnormal in the absence of symptoms.[26]

Common laboratory findings in patients with 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,[27,28] dermatologic,[29] hematologic,[30] hepatic,[31] neurologic,[32,33] renal,[34,35] and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients.[36]

The long-term sequelae of COVID-19 survivors are currently unknown. Persistent symptoms after recovery from acute COVID-19 have been described (see Clinical Spectrum of SARS-CoV-2 Infection). Lastly, SARS-CoV-2 infection has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children, or MIS-C).[37,38] Please see Special Considerations in Children for more information.

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Testing for SARS-CoV-2 Infection

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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

Diagnostic Testing for SARS-CoV-2 Infection

Everyone who has symptoms that are consistent with COVID-19, as well as people with known high-risk exposures to SARS-CoV-2, should be tested for SARS-CoV-2 infection. Such testing should employ either a nucleic acid amplification test (NAAT) or an antigen test to detect SARS-CoV-2. Ideally, diagnostic testing should also be performed for people who are likely to be at repeated risk of exposure to SARS-CoV-2, such as health care workers and first responders. Testing should also be considered for individuals who spend time in heavily populated environments (e.g., teachers, students, food industry workers) and for travelers. Testing requirements may vary by state, local, and employer policies. Travelers may need evidence of a recent negative test result to enter some states or countries; such documentation may be an acceptable alternative to quarantine upon arrival.

A number of diagnostic tests for SARS-CoV-2 infection (e.g., NAATs, antigen tests) have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA),[1] but no diagnostic test has been approved by the FDA.

Although nasopharyngeal specimens remain the recommended samples for SARS-CoV-2 diagnostic testing, nasal (anterior nares or mid-turbinate) or oropharyngeal swabs are acceptable alternatives.[2] Lower respiratory tract samples have a higher yield than upper tract samples, but they are often not obtained because of concerns about aerosolization of the virus during sample collection procedures. Some tests that have received EUAs can also be performed on saliva specimens. Studies are currently evaluating the use of other sample types, including stool samples.

Some tests that have received EUAs allow for self-collection of specimens at home, but these specimens

must be sent to a laboratory for processing. In addition, some tests allow trained personnel to collect and test specimens in nonclinical settings, such as in the home or in nursing or assisted living facilities. This allows real-time antigen results to be obtained on site.

Nucleic Acid Amplification Testing for SARS-CoV-2 Infection

Reverse transcriptase polymerase chain reaction (RT-PCR)-based diagnostic tests (which detect viral nucleic acids) are considered the gold standard for detecting current SARS-CoV-2 infection. More recently, NAATs have included a variety of additional platforms (e.g., reverse transcriptase loop-mediated isothermal amplification [RT-LAMP]). Clinically, there may be a window period of up to 5 days after exposure before viral nucleic acids can be detected. Diagnostically, some NAATs may produce false negative results if a mutation occurs in the part of the virus' genome that is assessed by that test.[3] The FDA monitors the potential effects of SARS-CoV-2 genetic variations on NAAT results and issues updates when specific variations could affect the performance of NAATs that have received EUAs. Generally, false negative results are more likely to occur when using NAATs that rely on only one genetic target. Therefore, a single negative test result does not exclude the possibility of SARS-CoV-2 infection in people who have a high likelihood of infection based on their exposure history and/or their clinical presentation.[4]

Many commercial NAATs that use RT-PCR rely on multiple targets to detect the virus, such that even if a mutation impacts one of the targets, the other RT-PCR targets will still work.[5] NAATs that use multiple targets are less likely to be impacted by an increased prevalence of genetic variants. In fact, because each of these tests target multiple locations on the virus' genome, they can be helpful in identifying new genetic variants before they become widespread in the population. For example, the B.1.1.7 variant that has been associated with increased transmission carries many mutations, including a double deletion at positions 69 and 70 on the spike protein gene (S-gene). This mutation appears to impact the detection of the S-gene but does not impact other genetic targets in certain NAATs. If COVID-19 is still suspected after a patient receives a negative test result, clinicians should consider repeating testing; ideally, they should use a NAAT with different genetic targets.[3]

SARS-CoV-2 poses several diagnostic challenges, including potentially discordant shedding of virus from the upper versus the lower respiratory tract. However, due to the high specificity of NAATs, a positive result on a NAAT of an upper respiratory tract sample from a patient with recent onset of SARS-CoV-2-compatible symptoms is sufficient to diagnose COVID-19. In patients with COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), lower respiratory tract specimens have a higher viral load and thus a higher yield than upper respiratory tract specimens.[6-12] For intubated or mechanically ventilated patients with clinical signs and symptoms that are consistent with COVID-19 pneumonia, the COVID-19 Treatment Guidelines Panel (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 (BAL) samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 **(BII)**.

BAL and sputum induction are aerosol-generating procedures that should be performed only after careful consideration of the risk of exposing staff to infectious aerosols. Endotracheal aspiration appears to carry a lower risk of aerosol-generation than BAL, and some experts consider the sensitivity and specificity of endotracheal aspirates and BAL specimens comparable in detecting SARS-CoV-2.

Nucleic Acid Amplification Testing for Individuals With a Previous Positive SARS-CoV-2 Test Result

NAATs can detect SARS-CoV-2 RNA in specimens obtained weeks to months after the onset of COVID-19 symptoms.[13,14] However, the likelihood of recovering replication-competent virus >10 days from the onset of symptoms in those with mild disease and >20 days in those with severe disease is very low.[15,16] Furthermore, both virologic studies and contact tracing of high-risk contacts show a low risk for SARS-CoV-2 transmission after these intervals.[17,18] Based on these results, the Centers for Disease Control and Prevention (CDC) recommends that NAATs should not be repeated in asymptomatic persons within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2 **(AIII)**.[19] If there are concerns that an immunocompromised health care worker may still be infectious >20 days from the onset of SARS-CoV-2 infection, consultation with local employee health services regarding return-to-work testing policies is advised.

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)**. However, it should be noted that persons infected with SARS-CoV-2 may have a negative result on an initial NAAT and then have a positive result on a subsequent test due to intermittent detection of viral RNA and not due to reinfection.[13] When the results for an initial and a subsequent test are positive, comparative viral sequence data from both tests are needed to distinguish between the persistent presence of viral fragments and reinfection. In the absence of viral sequence data, the cycle threshold (Ct) value from a positive NAAT result may provide information about whether a newly detected infection is related to the persistence of viral fragments or to reinfection. The Ct value is the number of PCR cycles at which the nucleic acid target in the sample becomes detectable. In general, the Ct value is inversely related to the SARS-CoV-2 viral load. Because the clinical utility of Ct values is an area of active investigation, an expert should be consulted if these values are used to guide clinical decisions.

Antigen Testing for SARS-CoV-2 Infection

Antigen-based diagnostic tests (which detect viral antigens) are less sensitive than RT-PCR-based tests, but they have similarly high specificity. Antigen tests perform best early in the course of symptomatic SARS-CoV-2 infection, when the viral load is thought to be highest. Advantages of antigen-based tests are their low cost and rapid turnaround time. The availability of immediate results makes them an attractive option for point-of-care testing in high-risk congregate settings where preventing transmission is critical. Antigen-based tests also allow for repeat testing to quickly identify persons with SARS-CoV-2 infection.

Increasingly, data are available to guide the use of antigen tests as screening tests to detect or exclude SARS-CoV-2 infection in asymptomatic persons, or to determine whether a person who was previously confirmed to have SARS-CoV-2 infection is still infectious. The CDC has developed an antigen testing algorithm for persons who have symptoms of COVID-19, those who are asymptomatic and have a close contact with COVID-19, and those who are asymptomatic and have no known exposure to a person with COVID-19.[20]

The CDC testing algorithm recommends additional NAATs when a person who is strongly suspected of having SARS-CoV-2 infection (i.e., a person who is symptomatic) receives a negative result, and when a person who is asymptomatic receives a positive result. Antigen tests can yield false positive results for a variety of reasons, including:

- Incomplete adherence to the instructions for antigen test performance (e.g., reading the results outside the specified time interval or storing test cartridges/cards inappropriately)

- Test interference due to human antibodies (e.g., rheumatoid factor or other nonspecific antibodies)
- Use in communities that have a low prevalence of SARS-CoV-2 infection

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

Unlike NAATs and antigen tests for SARS-CoV-2 that detect the presence of the virus, serologic or antibody tests can detect recent or prior SARS-CoV-2 infection. Because it may take 21 days or longer after symptom onset for seroconversion to occur (i.e., the development of detectable immunoglobulin [Ig] M and/or IgG antibodies to SARS-CoV-2),[21-26] the Panel **does not recommend** serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection **(AIII)**. Because NAATs and antigen tests for SARS-CoV-2 occasionally yield false negative results, serologic tests have been used in some settings as an additional diagnostic test for patients who are strongly suspected to have SARS-CoV-2 infection. Using a serologic test in combination with a NAAT to detect IgG or total antibodies 3 to 4 weeks after symptom onset maximizes the sensitivity and specificity to detect past infection.

No serologic tests for SARS-CoV-2 are approved by the FDA; some, but not all, commercially available serologic tests for SARS-CoV-2 have received EUAs from the FDA.[1] Several professional societies and federal agencies, including the Infectious Diseases Society of America, the CDC, and the FDA, provide guidance on the use of serologic testing for SARS-CoV-2.

Several factors should be considered when using serologic tests for SARS-CoV-2, including:

- Important performance characteristics of many of the commercially available serologic tests have not been fully characterized, including the sensitivity and specificity of these tests (i.e., the rates of true positive and true negative results). Serologic assays that have FDA EUAs should be used for public health and clinical use. Formal comparisons of serologic tests are in progress.
- Two types of serologic tests have received EUAs from the FDA. The first type are antibody tests that detect the presence of binding antibodies, which bind to a pathogen (e.g., a virus). The second type of tests detect neutralizing antibodies from recent or prior SARS-CoV-2 infection. It is unknown whether one type of test is more clinically meaningful than the other.
- Serologic assays may detect IgM, IgG, IgA, and/or total antibodies, or a combination of IgM and IgG antibodies. Serologic assays that detect IgG and total antibodies have higher specificity to detect past infection than assays that detect IgM and/or IgA antibodies or a combination of IgM and IgG antibodies.
- 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 SARS-CoV-2 antibodies are detected during a serologic test, the results should be interpreted with caution for the following reasons:

- It is unclear how long antibodies persist following infection; *and*
- It is unclear whether the presence of antibodies confers protective immunity against future infection.

In communities that have a low prevalence of SARS-CoV-2 infection, the proportion of positive test results that are false positives may be quite high. In these situations, confirmatory testing using a distinct antibody assay, ideally one that uses a different antigenic target (e.g., the nucleocapsid phosphoprotein

if the first assay targeted the spike protein), can substantially improve the probability that persons with positive test results are antibody positive.

Assuming that the test is reliable, serologic tests that identify recent or prior SARS-CoV-2 infection may be used to:

- Differentiate SARS-CoV-2 antibody responses to natural infection from vaccine-induced antibody responses to the SARS-CoV-2 spike protein antigen. Because nucleocapsid protein is not a constituent of vaccines that are currently available through EUAs or in late-stage clinical trials, serologic tests that detect antibodies by recognizing nucleocapsid protein can be used to distinguish antibody responses to natural infection from vaccine-induced antibody responses.

- Determine who may be eligible to donate convalescent plasma

- Estimate the proportion of the population that has been exposed to SARS-CoV-2

Based on current knowledge, serologic tests **should not be used** to **(AIII)**:

- Make decisions about how to group persons in congregate settings (e.g., schools, dormitories, correctional facilities)

- Determine whether persons may return to the workplace

- Assess for prior infection solely to determine whether to vaccinate an individual

- Assess for immunity to SARS-CoV-2 following vaccination, except in clinical trials

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Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: April 21, 2021

Summary Recommendations
• The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial **(AIII)**.
• The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 post-exposure prophylaxis (PEP) **(AI)**.
• The Panel **recommends against** the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial **(AIII)**.
• The Panel recommends that health care providers follow recommendations from the Advisory Committee on Immunization Practices when using SARS-CoV-2 vaccines **(AI)**.
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

General Prevention Measures

Transmission of SARS-CoV-2 is thought to mainly occur through respiratory droplets transmitted from an infectious person to others within six feet of the person. Less commonly, airborne transmission of small droplets and particles of SARS-CoV-2 to persons further than six feet away can occur, and in rare cases, people passing through a room that was previously occupied by an infectious person may become infected. SARS-CoV-2 infection via airborne transmission of small particles tends to occur after prolonged exposure (i.e., ≥30 minutes) to an infectious person who is in an enclosed space with poor ventilation.[1]

The risk of SARS-CoV-2 transmission can be reduced by covering coughs and sneezes and maintaining a distance of at least six feet from others. When consistent distancing is not possible, face coverings may further reduce the spread of infectious droplets from individuals with SARS-CoV-2 infection to others. Frequent handwashing also effectively reduces the risk of infection.[2] Health care providers should follow the Centers for Disease Control and Prevention (CDC) recommendations for infection control and appropriate use of personal protective equipment (PPE).[3]

Vaccines

Currently, no SARS-CoV-2 vaccine has been approved by the Food and Drug Administration (FDA). In December 2020, the FDA issued Emergency Use Authorizations for two mRNA vaccines, BNT162b2 (Pfizer-BioNTech)[4] and mRNA-1273 (Moderna).[5] In February 2021, FDA issued an EUA for a human adenovirus type 26 (Ad26) vectored vaccine, Ad26.COV2.S (Johnson & Johnson/Janssen).[6] BNT162b2 can be administered to individuals aged ≥16 years, whereas mRNA-1273 and Ad26.COV2.S can be given to individuals aged ≥18 years. Clinical trials for these vaccines in younger age groups are currently underway.

In large, placebo-controlled trials, the mRNA-1273 and BNT162b2 vaccines were 94% and 95% efficacious, respectively, in preventing symptomatic laboratory-confirmed COVID-19 after participants completed a two-dose series. The Ad26.COV2.S vaccine was 66% efficacious in preventing moderate to severe/critical laboratory-confirmed COVID-19 after a single vaccine dose. Cases of COVID-19 were confirmed by the presence of symptoms and a positive result on a SARS-CoV-2 nucleic acid amplification test (NAAT).[6-8] All three vaccines also showed high efficacy against severe COVID-19. Local and systemic adverse events are relatively common with these vaccines, especially after the second dose. Most adverse events that occurred in vaccine trials were mild or moderate in severity (i.e.,

they did not prevent vaccinees from engaging in daily activities). There have been a few reports of severe allergic reactions following SARS-CoV-2 vaccination, including some reports of patients who experienced anaphylaxis after receiving a SARS-CoV-2 mRNA vaccine.[6,9] Safety data continue to be collected. Certain populations, such as pregnant and lactating individuals, were not included in the initial vaccine trials. The American College of Obstetricians and Gynecologists has published interim guidance on the use of the SARS-CoV-2 mRNA vaccines in pregnant and lactating people.[10]

It is not known how long the protective effect of SARS-CoV-2 vaccines will last or whether SARS-CoV-2 vaccines can prevent asymptomatic infection or transmission, whether they will prevent infection by all current or emergent strains of SARS-CoV-2, whether they will be effective in immunocompromised patients, or whether they will work as well in patients who are at high risk for severe COVID-19 as in those who are at low risk. The efficacy and safety of SARS-CoV-2 vaccines have not been established in children, pregnant people, or immunocompromised patients. Clinical trials for other SARS-CoV-2 vaccine candidates are ongoing.

CDC sets the adult and childhood immunization schedules for the United States based on recommendations from the Advisory Committee on Immunization Practices (ACIP). ACIP considers disease epidemiology, burden of disease, vaccine efficacy and effectiveness, vaccine safety, the quality of the available evidence, and potential vaccination implementation issues. ACIP also sets priorities regarding who receives vaccines in the event of a shortage. ACIP COVID-19 vaccine recommendations are reviewed by CDC's Director and, if adopted, are published as official CDC recommendations in the *Morbidity and Mortality Weekly Report*.[11]

Pre-Exposure Prophylaxis

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

Rationale

At present, there is no known agent that can be administered before exposure to SARS-CoV-2 (i.e., as PrEP) to prevent infection. Clinical trials are investigating several agents, including emtricitabine plus tenofovir alafenamide or tenofovir disoproxil fumarate, hydroxychloroquine, ivermectin, 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.

Clinical Trial Data

Randomized Controlled Trial of Hydroxychloroquine for SARS-CoV-2 Pre-Exposure Prophylaxis Among Health Care Workers

This double-blind, placebo-controlled, randomized trial was designed to determine whether hydroxychloroquine 600 mg per day reduced the frequency of SARS-CoV-2 infection over an 8-week period in hospital-based health care workers. The primary outcome was incidence of SARS-CoV-2 infection as determined by reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasopharyngeal swabs collected at 4 and 8 weeks or the occurrence of COVID-19 symptoms.[12]

Study Population

- Participants included health care workers at two Philadelphia hospitals who worked ≥20 hours per week in a hospital-based unit, had no known history of SARS-CoV-2 infection, and had no COVID-19-like symptoms in the 2 weeks before enrollment. The study enrolled workers in the emergency department and in dedicated COVID-19 treatment units.
- The study excluded individuals who were allergic to hydroxychloroquine and those with glucose-6-phosphate dehydrogenase deficiency, retinal disease, or substantial cardiac disease.

Results

- The study was based on an assumed 10% infection rate for the planned inclusion of 100 participants per arm.
- Between April 9 and July 14, 2020, community SARS-CoV-2 infection rates declined. At the time of the second interim analysis (when 125 of 132 participants who provided consent were evaluable for the primary endpoint), the Data Safety Monitoring Board recommended early termination of the study for futility.
- Four participants in each group developed SARS-CoV-2 infection (positivity rate of 6.3% vs. 6.6% in the hydroxychloroquine and placebo groups, respectively; $P > 0.99$). Across the groups, six participants developed symptoms of COVID-19, but none required hospitalization.
- Serologic testing for anti-spike protein immunoglobulin (Ig) M, IgG, and nucleocapsid protein IgG demonstrated more positive results among participants in the hydroxychloroquine group (four participants [7.4%]) than in the placebo group (two participants [3.7%]), although the difference was not statistically significant ($P = 0.40$).
- Mild adverse events were more common among participants in the hydroxychloroquine group (45%) than in the placebo group (26%; $P = 0.04$). The greatest difference was the increased frequency of mild diarrhea in the hydroxychloroquine group.
- The rates of treatment discontinuation were similar in the hydroxychloroquine group (19%) and the placebo group (16%).
- There were no cardiac events in either arm and also no significant difference in the median frequency of changes in QTc between the study arms ($P = 0.98$).

Limitations

- The study was stopped early.
- Due to the low SARS-CoV-2 infection rate among the participants, the study was underpowered to detect a prophylactic benefit of hydroxychloroquine.
- The study population was mostly young, healthy health care workers; therefore, whether the study findings are applicable to other populations is uncertain.

Interpretation

There was no clinical benefit of administering hydroxychloroquine 600 mg per day for 8 weeks as PrEP to health care workers who were exposed to patients with COVID-19. Compared to placebo, hydroxychloroquine was associated with an increased risk of mostly mild adverse events.

Hydroxychloroquine as Pre-Exposure Prophylaxis for COVID-19 in Health Care Workers: A Randomized Trial (COVID PREP Study)

This double-blind, placebo-controlled, randomized clinical trial investigated whether hydroxychloroquine 400 mg given once- or twice-weekly for 12 weeks can prevent SARS-CoV-2 infection in health care workers at high-risk of exposure. The primary outcome was COVID-19-free survival time. Diagnosis of COVID-19 was defined as having laboratory-confirmed SARS-CoV-2 infection or having cough, shortness of breath, or difficulty breathing or having two or more of the following symptoms: fever, chills, rigors, myalgia, headache, sore throat, or new olfactory and taste disorders. COVID-19-compatible illness was included as a primary outcome even if a SARS-CoV-2 PCR test was not performed or if it was performed and the result was negative.[13]

Study Population

- The study participants had to be working in the emergency department, in the intensive care unit, on a dedicated COVID-19 hospital ward, or as a first responder; alternatively, they had to have a

job description that included regularly performing aerosol-generating procedures.

- Participants were recruited via social media platforms. Informed consent was obtained remotely, and the study drug was delivered to the participants by couriers.

Results

- The study was powered based on an anticipated 10% event rate of new symptomatic infections. The investigators determined that the study needed to enroll 1,050 participants per arm to have 80% power. However, it became apparent before the first interim analysis that the study would not meet the enrollment target. As a result, enrollment was stopped without unblinding. The investigators attributed the marked decline in enrollment to the negative reports related to the safety of hydroxychloroquine, including a warning from the FDA.

- Among the 1,483 participants who were randomized, baseline characteristics were similar across the study arms.

- The number of individuals who met the primary endpoint of confirmed or suspected SARS-CoV-2 infection was 39 (7.9%) in the placebo group and 29 (5.9%) in both the once- and twice-weekly hydroxychloroquine groups. Among the 97 participants, only 17 were confirmed to be SARS-CoV-2 PCR positive.

- Compared to placebo, the hazard ratio for the primary endpoint was 0.72 (95% CI, 0.4–1.16; P = 0.18) for the once-weekly hydroxychloroquine arm and 0.74 (95% CI, 0.46–1.19; P = 0.22) for the twice-weekly hydroxychloroquine arm.

- There were no significant differences for any of the secondary efficacy endpoints among the three groups.

- There were significantly more adverse events reported in the once- and twice-weekly hydroxychloroquine arms (occurred in 31% vs. 36% of participants, respectively; $P < 0.001$ for both groups) than in the placebo group (occurred in 21% of participants). The most common side effects were upset stomach and nausea.

- Drug concentrations were measured in dried whole blood samples from a subset of 180 participants who received hydroxychloroquine. The median hydroxychloroquine concentrations for the twice- and once-weekly hydroxychloroquine groups were 200 ng/mL and 98 ng/mL, respectively; both concentrations are substantially below the in vitro half-maximal effective concentration (EC_{50}) of hydroxychloroquine. The investigators noted that the simulations that were used to determine the hydroxychloroquine dose for the study predicted much higher drug concentrations than the observed levels.

Limitations

- The study was prematurely halted due to poor enrollment; therefore, the study population was insufficient to detect differences in outcomes among the study arms.

- The study only assessed the SARS-CoV-2 inhibitory activity of two doses of hydroxychloroquine, neither of which achieved concentrations that exceeded the in vitro EC_{50} of the drug.

- Only 17.5% of the participants who met study endpoints had positive SARS-CoV-2 test results; the remainder had COVID-19-compatible symptoms without a confirmatory diagnosis.

Interpretation

Hydroxychloroquine 400 mg once- or twice-weekly did not reduce the incidence of documented SARS-CoV-2 infection or COVID-19-compatible symptoms among health care workers who were at a high risk of infection. These findings suggest that hydroxychloroquine was not effective for SARS-CoV-2 PrEP or that the dose used for PrEP was suboptimal.

Post-Exposure Prophylaxis

- The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 post-exposure prophylaxis (PEP) **(AI)**.
- The Panel **recommends against** the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial **(AIII)**.

Rationale

Several randomized controlled trials have evaluated the use of hydroxychloroquine for SARS-CoV-2 PEP.[14-16] None of these studies have reported any evidence of efficacy, and all showed a higher frequency of adverse events among participants who received hydroxychloroquine than among control participants. The results of some of these studies are described below.

A number of agents (e.g., anti-SARS-CoV-2 monoclonal antibodies, hyperimmune gammaglobulin, convalescent plasma, ivermectin, interferons, tenofovir with or without emtricitabine, vitamin D) are currently being investigated for SARS-CoV-2 PEP. The latest clinical trials for SARS-CoV-2 PEP can be found at *ClinicalTrials.gov*.

Clinical Trial Data

Both chloroquine and hydroxychloroquine have in vitro activity against severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and SARS-CoV-2.[17,18] A small cohort study without a control group suggested that hydroxychloroquine might reduce the risk of SARS-CoV-2 transmission to close contacts.[19]

Household-Randomized, Double-Blind Controlled Trial of SARS-CoV-2 Post-Exposure Prophylaxis With Hydroxychloroquine

A household-randomized, double-blind controlled trial evaluated the use of hydroxychloroquine as PEP to prevent SARS-CoV-2 infection. The study was conducted at seven institutions in the United States between March and August 2020. Participants were recruited using online advertising, social media, and referrals from hospitals, health departments, and individuals with laboratory-confirmed SARS-CoV-2 infection.[14]

Households were randomized to receive oral hydroxychloroquine 400 mg once daily for 3 days, followed by hydroxychloroquine 200 mg once daily for an additional 11 days, or oral ascorbic acid 500 mg once daily for 3 days, followed by ascorbic acid 250 mg once daily for 11 days. Mid-turbinate nasal swabs were collected daily during the first 14 days, with the primary endpoint being PCR-confirmed SARS-CoV-2 infection within 14 days after enrollment in those who were not infected at baseline.

Study Population
- Eligible participants had close contact with a SARS-CoV-2-infected person, which included household contacts or other close contacts (82%) or health care workers (18%) who cared for an infected person without wearing appropriate PPE. Participants must have come into contact with an index person who had received a diagnosis of SARS-CoV-2 infection within the past 14 days, and high-risk exposure to the index people must have occurred within the previous 96 hours.
- Enrollment included 829 participants from 671 households; 407 participants (in 337 households) received hydroxychloroquine, and 422 participants (in 334 households) received ascorbic acid.

Results
- A total of 98 SARS-CoV-2 infections were detected during the first 14 days of follow-up, with an overall cumulative incidence of 14.3% (95% CI, 11.5% to 17%). Fifty-three events (i.e., PCR-

confirmed SARS-CoV-2 infection) occurred in the hydroxychloroquine group, and 45 events occurred in the control group (aHR 1.10; 95% CI, 0.73–1.66; $P > 0.20$)

- In preplanned analyses, hazard ratios were not significantly different within subgroups based on type of contact, time between the most recent contact and the first dose of the study drug, duration of contact, number of contacts enrolled within the household, quarantine status, index case symptoms, or number of adults or children in the household.

- Adverse events that are associated with the use of hydroxychloroquine, including gastrointestinal symptoms and rash, occurred in 112 participants: 66 participants (16.2%) in the hydroxychloroquine group and 46 participants (10.9%) in the control group ($P = 0.026$).

Limitations

- There was an average window of 2 days between the time of the most recent exposure to the index people and the time the study drugs were administered. The lapse of time between exposure to SARS-CoV-2 and initiation of hydroxychloroquine may have affected the efficacy of the drug as PEP.

- The primary analysis excluded approximately 10% of enrolled people who were shown to have SARS-CoV-2 infection at baseline.

Interpretation

In this study, hydroxychloroquine was ineffective when used as PEP for SARS-CoV-2 infection. Participants who received hydroxychloroquine had an expected greater risk of adverse events than those who received ascorbic acid.

Double-Blind Randomized Controlled Trial of Hydroxychloroquine as Post-Exposure Prophylaxis in Contacts With High-Risk or Moderate-Risk Occupational or Household Exposures

This double-blind randomized controlled trial included 821 participants who self-enrolled in the study using an internet-based survey. Participants were randomized to receive either hydroxychloroquine (hydroxychloroquine 800 mg once, followed by hydroxychloroquine 600 mg 6 to 8 hours later, and then hydroxychloroquine 600 mg once daily for 4 additional days) or placebo. Because enrollment was done online, the study drugs were sent to participants by overnight mail, and consequently, more than 50% of the participants started the first dose of their assigned treatment 3 to 4 days after exposure to SARS-CoV-2.[16]

Study Population

- Participants had a high or moderate risk of occupational exposure (66% of participants) or household exposure (34% of participants) to SARS-CoV-2.

- High-risk exposure was defined as being within six 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). Moderate-risk exposure was defined as exposure from the same distance and for the same duration while wearing a face mask but no eye shield (12.4% of participants).

Results

- A total of 107 participants developed the primary outcome of symptomatic illness. Illness was confirmed by a positive result on a SARS-CoV-2 molecular test. If testing was not available, participants were considered to have symptomatic illness if they developed a compatible COVID-19-related syndrome based on CDC criteria.

- Due to limited access to molecular diagnostic testing, SARS-CoV-2 infection was confirmed in only 16 of the 107 participants (15%). There was no statistically significant difference in the

incidence of the primary outcome (symptomatic illness) between the hydroxychloroquine group and the placebo group (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), and no serious adverse reactions or cardiac arrhythmias in either group.

Limitations

- Most participants did not start their assigned therapy until at least 3 days after exposure to SARS-CoV-2.
- Only 15% of participants who reached the primary outcome had SARS-CoV-2 infection confirmed by molecular diagnostics.
- The study participants were young (median age 40 years) and had a relatively low risk of severe COVID-19.

Interpretation

There was no difference in the incidence of observed symptomatic COVID-19 between participants who received hydroxychloroquine 600 mg once daily and those who received placebo. Although hydroxychloroquine 600 mg per day was associated with an increased frequency of adverse events, these adverse events were mostly mild.

Cluster-Randomized Trial of SARS-CoV-2 Post-Exposure Prophylaxis With Hydroxychloroquine

This open-label, cluster-randomized trial included 2,314 asymptomatic contacts of 672 COVID-19 cases in Spain.[15] Participants who were epidemiologically linked to a PCR-positive COVID-19 case were defined as study clusters (called rings). All contacts in a ring were simultaneously cluster-randomized in a 1:1 ratio to the control arm (usual care) or the intervention arm (hydroxychloroquine 800 mg once daily for 1 day, followed by hydroxychloroquine 400 mg once daily for 6 days). Participants were informed of their allocated study arm after being randomized to the intervention or control arm and signing a consent form.

The primary outcome was onset of laboratory-confirmed COVID-19, which was defined as a positive result on a SARS-CoV-2 PCR test and at least one of the following symptoms: fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory and taste disorders, or diarrhea. A secondary outcome was onset of SARS-CoV-2 infection, which was defined as either a positive SARS-CoV-2 PCR test result or the presence of any of the symptoms compatible with COVID-19. An additional secondary outcome was development of serological positivity at Day 14.

Study Population

- Study participants were health care or nursing home workers (60.3%), household contacts (27.1%), or nursing home residents (12.7%) who were documented to have spent >15 minutes within two meters of a PCR-positive COVID-19 case during the 7 days prior to enrollment.
- The baseline characteristics of the participants were similar between the two study arms, including comorbidities, number of days of exposure to SARS-CoV-2 before enrollment and randomization, and type of contact.

Results

- A total of 138 study participants (6.0%) developed PCR-confirmed, symptomatic SARS-CoV-2 infection. There was no statistical difference in the incidence of confirmed infection between the hydroxychloroquine and control arms (5.7% vs. 6.2%, respectively; risk ratio 0.86; 95% CI, 0.52–1.42).

- There was no statistical difference between the study arms in the incidence of either PCR-confirmed or symptomatically compatible COVID-19, which was 18.2% overall (18.7% in the hydroxychloroquine arm vs. 17.8% in the control arm; risk ratio 1.03; 95% CI, 0.77–1.38).
- There was no statistical difference between the arms in the rate of positivity for SARS-CoV-2 IgM and/or IgG (14.3% in the hydroxychloroquine arm vs. 8.7% in the control arm; risk ratio 1.57; 95% CI, 0.94–2.62).
- There were more adverse events among the hydroxychloroquine-treated participants (56.1%) than among the control participants (5.9%), although most of the adverse events were mild. Common adverse events included gastrointestinal events, nervous system disorders, myalgia, fatigue, and malaise. No serious adverse events were attributed to the study drug.

Limitations
- The study lacked a placebo comparator, which could have had an impact on safety reporting.
- Data regarding the extent of the exposure to the index cases was limited.
- For >50% of the study participants, the time from exposure to the index case to randomization was ≥4 days.

Interpretation

The hydroxychloroquine regimen used for PEP in this study did not prevent SARS-CoV-2 infection in healthy individuals who were exposed to a PCR-positive case.

Ivermectin

High concentrations of ivermectin have been shown to inhibit SARS-CoV-2 replication in vitro.[20,21] Population data also indicate that country-wide mass use of prophylactic chemotherapy for parasitic infections, including the use of ivermectin, is associated with a lower incidence of COVID-19.[22] At this time, there are limited clinical trials regarding the safety and efficacy of ivermectin for SARS-CoV-2 PrEP or PEP. Although several studies have reported potentially promising results, the findings are limited by the design of the studies, their small sample sizes, and lack of details regarding the safety and efficacy of ivermectin. The results of these trials are described below.

In a descriptive, uncontrolled interventional study of 33 contacts of patients with laboratory-confirmed COVID-19, no cases of SARS-CoV-2 infection were identified within 21 days of initiating ivermectin for PEP.[23] An open-label, randomized controlled trial investigated ivermectin prophylaxis (plus personal protective measures [PPMs]) in health care workers (as PrEP) or in household contacts (as PEP) exposed to patients with laboratory-confirmed COVID-19. The incidence of SARS-CoV-2 infection was lower among the participants who received ivermectin than among control participants who used only PPMs. However, the study provided no data on the characteristics of the study participants, types of exposures, or how endpoints were defined.[24] Finally, in a small case-control study in SARS-CoV-2-exposed health care workers, 186 participants who became infected were matched with 186 uninfected controls. Of those who received ivermectin after exposure to SARS-CoV-2, 38 were in the infected group and 77 were in the uninfected group, which led the investigators to conclude that ivermectin reduced the incidence of SARS-CoV-2 infection.[25]

Additional studies of ivermectin for SARS-CoV-2 are ongoing. Please see *ClinicalTrials.gov* for the latest information.

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Clinical Spectrum of SARS-CoV-2 Infection

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Patients with 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 presentation of SARS-CoV-2-infected individuals according to illness severity.

In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories. However, the criteria for each category may overlap or vary across clinical guidelines and clinical trials, and a patient's clinical status may change over time.

Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but who have no symptoms that are consistent with COVID-19.

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, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.

Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level.

Severe Illness: Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.

Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Patients with certain underlying comorbidities are at a higher risk of progressing to severe COVID-19. These comorbidities include being aged 65 years or older; having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, or chronic kidney disease; being pregnant; being a cigarette smoker; and being a recipient of transplant or immunosuppressive therapy.[1] Health care providers should monitor such patients closely until clinical recovery is achieved.

The optimal pulmonary imaging technique has not yet been defined for people with symptomatic SARS-CoV-2 infection. Initial evaluation for these patients may include chest X-ray, ultrasound, or, if indicated, computed tomography. An electrocardiogram should be performed if indicated. Laboratory testing includes a complete blood count with differential and a metabolic profile, including liver and renal function tests. Although inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin are not routinely measured as part of standard care, results from such measurements may have prognostic value.[2-4]

The definitions for the severity of illness categories listed above also apply to pregnant patients. However, the threshold for certain interventions may be different for pregnant patients and nonpregnant patients. For example, oxygen supplementation is recommended for pregnant patients when SpO_2 falls below 95% on room air at sea level to accommodate physiologic changes in oxygen demand during pregnancy and to ensure adequate oxygen delivery to the fetus.[5] If laboratory parameters are used for monitoring pregnant patients and making decisions about interventions, clinicians should be aware that normal physiologic changes during pregnancy can alter several laboratory values. In general, leukocyte cell count increases throughout gestation and delivery and peaks during the immediate postpartum period. This increase is mainly due to neutrophilia.[6] D-dimer and CRP levels also increase during

pregnancy and are often higher in pregnant patients than nonpregnant patients.[7] Detailed information on treating COVID-19 in pregnant patients can be found in Special Considerations in Pregnancy and in the pregnancy considerations subsection of each individual section of the Guidelines.

In pediatric patients, radiographic abnormalities are common and, for the most part, should not be the only criteria used to determine the severity of illness. The normal values for respiratory rate also vary with age in children; thus, hypoxia should be the primary criterion used to define severe COVID-19, especially in younger children. In a small number of children and in some young adults, SARS-CoV-2 infection may be followed by a severe inflammatory condition called multisystem inflammatory syndrome in children (MIS-C).[8,9] This syndrome is discussed in detail in Special Considerations in 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 what percentage of individuals who present with asymptomatic infection progress to clinical disease. Some asymptomatic individuals have been reported to have objective radiographic findings that are consistent with COVID-19 pneumonia.[10,11] 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 infection. See Therapeutic Management of Adults With COVID-19 for recommendations regarding SARS-CoV-2–specific therapy.

Mild Illness

Patients with mild illness may exhibit a variety of signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell). They do not have 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 telephone visits. No imaging or specific laboratory evaluations are routinely indicated in otherwise healthy patients with mild COVID-19. Older patients and those with underlying comorbidities are at higher risk of disease progression; therefore, health care providers should monitor these patients closely until clinical recovery is achieved. See Therapeutic Management of Adults With COVID-19 for recommendations regarding SARS-CoV-2-specific therapy.

Moderate Illness

Moderate illness is defined as evidence of lower respiratory disease during clinical assessment or imaging, with SpO_2 ≥94% on room air at sea level. Given that pulmonary disease can progress rapidly in patients with COVID-19, patients with moderate disease should be closely monitored. If bacterial pneumonia or sepsis is suspected, administer empiric antibiotic treatment, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection. See Therapeutic Management of Adults With COVID-19 for recommendations regarding SARS-CoV-2–specific therapy.

Severe Illness

Patients with COVID-19 are considered to have severe illness if they have SpO_2 <94% on room air at sea level, a respiratory rate >30 breaths/min, PaO_2/FiO_2 <300 mm Hg, or lung infiltrates >50%. These patients may experience rapid clinical deterioration. Oxygen therapy should be administered immediately using a nasal cannula or a high-flow oxygen device. See Therapeutic Management of Adults With COVID-19 for recommendations regarding SARS-CoV-2-specific therapy. If secondary bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate the patient daily,

and de-escalate or stop antibiotics if there is no evidence of bacterial infection.

Critical Illness

Critically ill patients may have acute respiratory distress syndrome, septic shock that may represent virus-induced distributive shock, cardiac dysfunction, an exaggerated inflammatory response, and/or exacerbation of underlying comorbidities. In addition to pulmonary disease, patients with critical illness may also experience cardiac, hepatic, renal, central nervous system, or thrombotic disease.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 includes treating both the medical condition that initially resulted in ICU admission and other comorbidities and nosocomial complications.

For more information, see Care of Critically Ill Patients With COVID-19.

SARS-CoV-2 Reinfection

As seen with other viral infections, reinfection with SARS-CoV-2 after recovery from prior infection has been reported.[12] The true prevalence of reinfection is not known, although there are concerns that it may occur with increased frequency with the circulation of new variants.[13] SARS-CoV-2 can often be detected from nasal swab for weeks to months after initial infection, therefore, repeat testing to evaluate for reinfection should be considered only for those who have recovered from initial infection and present with COVID-19-compatible symptoms with no obvious alternate etiology **(AIII)**.[14] Diagnostic testing in this setting is summarized in Testing for SARS-CoV-2 Infection. In addition, if reinfection is suspected, guidelines for the diagnosis and evaluation of suspected SARS-CoV-2 reinfection are provided by the Centers for Disease Control and Prevention (CDC).[15]

It has been speculated that reinfection may occur more frequently in those with a less robust immune response during the initial infection, as is often reported in those with mild illness. Reinfection may also occur as initial immune responses wane over time. Nevertheless, one review noted that SARS-CoV-2 reinfection occurred after previous severe disease in three cases and as early as 3 weeks after diagnosis of the initial infection.[16] A public site posts a variety of published and unpublished reports of reinfection, noting that it has been described to occur from as early as a few weeks to many months after initial infection, and occasionally follows episodes of severe COVID-19.[17] Although data are limited, there is no evidence to suggest that the treatment of highly suspected or documented SARS-CoV-2 reinfection should be different from that for initial infection as outlined in Therapeutic Management of Adults With COVID-19.

Persistent Symptoms or Organ Dysfunction After Acute COVID-19

There have been an increasing number of reports of patients who experience persistent symptoms and/or organ dysfunction after acute COVID-19. Data about the incidence, natural history, and etiology of these symptoms are emerging. However, these reports have several limitations, including lack of an agreed-upon case definition and potential bias as most reports included only patients who attended post-COVID-19 clinics and no comparator groups. No specific treatments for the persistent effects of COVID-19 have yet been identified, although this COVID-19 rapid guideline proposes general management strategies.

The nomenclature for this phenomenon is evolving, and there is no established clinical terminology to date. It has been referred to as post-COVID-19 condition or colloquially, "long COVID," and affected patients have been referred to as "long haulers." The term "post-acute sequelae of COVID-19" (PASC) has also been used to describe late sequelae of SARS-CoV-2 infection that include these persistent

symptoms, as well as other delayed syndromes such as MIS-C and multisystem inflammatory syndrome in adults (MIS-A). To date, no case definition and no specific time frame have been established to define the syndrome of persistent symptoms and/or organ dysfunction after acute COVID-19. However, CDC recently proposed defining late sequelae as sequelae that extend >4 weeks after initial infection.[18,19] The Patient-Led Research Collaborative for COVID-19 defines long COVID as a collection of symptoms that develop during or following a confirmed or suspected case of COVID-19 and that continue for >28 days.[20] Incidence rates vary widely, from about 10% in some reports to one cohort study in which 87% of patients reported at least one persistent symptom.[21]

Some of the symptoms overlap with the post-intensive care syndrome (PICS) that has been described in patients without COVID-19, but prolonged symptoms and disabilities after COVID-19 have also been reported in patients with milder illness, including outpatients (see General Considerations for information on PICS).[22,23]

Despite limitations of the available descriptive data related to these persistent symptoms, some representative studies have suggested that common findings include fatigue, joint pain, chest pain, palpitations, shortness of breath, cognitive impairment, and worsened quality of life.[24,25]

CDC conducted a telephone survey of a random sample of 292 adult outpatients who had positive polymerase chain reaction results for SARS-CoV-2. Among the 274 respondents who were symptomatic at the time of testing, 35% reported not having returned to their usual state of health 2 weeks or more after testing; 26% among patients aged 18 to 34 years, 32% among those aged 35 to 49 years, and 47% among those aged ≥50 years.[23] An age of ≥50 years and the presence of three or more chronic medical conditions were associated with not returning to usual health within 14 to 21 days. Moreover, one in five individuals aged 18 to 34 years who did not have chronic medical conditions had not returned to baseline health when interviewed at a median of 16 days from the testing date.

In a cohort study from Wuhan, China, 1,733 discharged patients with COVID-19 were evaluated for persistent symptoms at a median of 186 days after symptom onset.[26] The most common symptoms were fatigue or muscle weakness and sleep difficulties (reported among 63% and 26% of participants, respectively). Anxiety or depression was reported among 23% of patients.

In a longitudinal prospective cohort of mostly outpatients with laboratory-confirmed SARS-CoV-2 infection at the University of Washington, 177 participants completed a follow-up questionnaire between 3 and 9 months after illness onset.[27] Overall, 91% of the respondents were outpatients (150 with mild illness and 11 with no symptoms), and only 9.0% had moderate or severe disease requiring hospitalization. Among those reporting symptoms, 33% of the outpatients and 31% of the hospitalized patients reported at least one persistent symptom. Persistent symptoms were reported by 27% of the patients aged 18 to 39 years, 30% aged 40 to 64 years, and 43% aged ≥65 years. The most common persistent symptoms were loss of sense of smell or taste and fatigue (both reported by 14% of participants).

Fatigue

The prevalence of fatigue among 128 individuals from Ireland who had recovered from the acute phase of COVID-19 was examined using the Chalder Fatigue Scale (CFQ11). More than half of patients (67 of 128 patients [52.3%]) reported persistent fatigue at a median of 10 weeks after initial symptoms first appeared. There was no association between illness severity and fatigue.[28] An outpatient service for patients recovering from acute COVID-19 developed in Italy reported that 87% of 143 patients surveyed reported persistent symptoms at a mean of 60 days after symptom onset, with the most common symptom being fatigue (which occurred in 53.1% of these patients).[21]

Cardiopulmonary

A study from the United Kingdom reported that among 100 hospitalized patients (32 received care in the ICU and 68 received care in hospital wards only), 72% of the ICU patients and 60% of the ward patients experienced fatigue and breathlessness at 4 to 8 weeks after hospital discharge. The authors suggested that posthospital rehabilitation may be necessary for some of these patients.[24] A retrospective study from China found that pulmonary function (as measured by spirometry) was still impaired 1 month after hospital discharge in 31 of 57 patients (54.4%).[29] In a study from Germany that included 100 patients who had recently recovered from COVID-19, cardiac magnetic resonance imaging (MRI) performed a median of 71 days after diagnosis revealed cardiac involvement in 78% of patients and ongoing myocardial inflammation in 60% of patients.[30] A retrospective study from China of 26 patients who had recovered from COVID-19 and who had initially presented with cardiac symptoms found abnormalities on cardiac MRI in 15 patients (58%).[31] The assessment of the prevalence of cardiac abnormalities in people with post-acute COVID-19 syndrome should be viewed with caution, however, as the analysis included only patients with cardiac symptoms.

Neuropsychiatric

Neurologic and psychiatric symptoms have also been reported among patients who have recovered from acute COVID-19. High rates of anxiety and depression have been reported in some patients using self-report scales for psychiatric distress.[25,32] Younger patients have been reported to experience more psychiatric symptoms than patients aged >60 years.[24,25] Patients may continue to experience headaches, vision changes, hearing loss, loss of taste or smell, impaired mobility, numbness in extremities, tremors, myalgia, memory loss, cognitive impairment, and mood changes for up to 3 months after diagnosis of COVID-19.[33-35] One study in the United Kingdom administered cognitive tests to 84,285 participants who had recovered from suspected or confirmed SARS-CoV-2 infection. These participants had worse performances across multiple domains than would be expected for people with the same ages and demographic profiles; this effect was observed even among those who had not been hospitalized.[36] However, the study authors did not report when the tests were administered in relation to the diagnosis of COVID-19.

Persistent symptoms after acute COVID-19 have also been reported in pregnant people.[37] Systematic data on persistent symptoms in children following recovery from the acute phase of COVID-19 are not currently available, although case reports suggest that children may experience long-term effects similar to those experienced by adults after clinical COVID-19.[38,39] MIS-C is discussed in Special Considerations in Children.

More research and more rigorous observational cohort studies are needed to better understand the pathophysiology and clinical course of these post-acute COVID-19 sequelae and to identify management strategies for patients. More information about ongoing studies can be found at *ClinicalTrials.gov*.

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