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. 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 measured by pulse oximetry (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, a respiratory rate >30 breaths/min, or lung infiltrates >50%.
- **Critical illness:** Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

SpO$_2$ is a key parameter for defining the illness categories listed above. However, pulse oximetry has important limitations (discussed in more detail below). Clinicians who use SpO$_2$ when assessing a patient must be aware of those limitations and conduct the assessment in the context of that patient’s clinical status.

Patients who are aged ≥65 years are at a higher risk of progressing to severe COVID-19. Other underlying conditions associated with a higher risk of severe COVID-19 include asthma, cancer, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes, advanced or untreated HIV infection, obesity, pregnancy, cigarette smoking, and being a recipient of immunosuppressive therapy or a transplant.1 Health care providers should closely monitor patients with these conditions until they achieve clinical recovery.

The initial evaluation for patients may include chest imaging (e.g., X-ray, ultrasound or computed tomography scan) and an electrocardiogram. Laboratory testing should include 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 also apply to pregnant patients. However, the threshold for certain interventions is different for pregnant patients and nonpregnant patients. For example, oxygen supplementation for pregnant patients is generally used when SpO$_2$ falls below 95% on room air at sea level to accommodate the 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. D-dimer and CRP levels also increase during pregnancy and are often higher in pregnant patients than nonpregnant patients. Detailed information on treating COVID-19 in pregnant patients can be found in Special Considerations in Pregnancy and in the pregnancy considerations subsections in 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; therefore, hypoxemia should be the primary criterion used to define severe COVID-19, especially in younger children. In a small subset of children and young adults, SARS-CoV-2 infection may be followed by the severe inflammatory condition multisystem inflammatory syndrome in children (MIS-C). This syndrome is discussed in detail in Special Considerations in Children.

Clinical Considerations for the Use of Pulse Oximetry

During the COVID-19 pandemic, the use of pulse oximetry to assess and monitor patients’ oxygenation status increased in hospital, outpatient health care facility, and home settings. Although pulse oximetry is useful for estimating blood oxygen levels, pulse oximeters may not accurately detect hypoxemia under certain circumstances. To avoid delays in recognizing hypoxemia, clinicians who use pulse oximetry to assist with clinical decisions should keep these limitations in mind.

Pulse oximetry results can be affected by skin pigmentation, thickness, or temperature. Poor blood circulation or the use of tobacco or fingernail polish also may affect results. The Food and Drug Administration (FDA) advises clinicians to refer to the label or manufacturer website of a pulse oximeter or sensor to ascertain its accuracy. The FDA also advises using pulse oximetry only as an estimate of blood oxygen saturation, because an SpO₂ reading represents a range of arterial oxygen saturation (SaO₂). For example, an SpO₂ reading of 90% may represent a range of SaO₂ from 86% to 94%.

Several published reports have compared measurements of SpO₂ and SaO₂ in patients with and without COVID-19. The studies demonstrated that occult hypoxemia (defined as SaO₂ <88% despite SpO₂ >92%) was more common in patients with darker skin pigmentation, which may result in adverse consequences. The likelihood of error was greater in the lower ranges of SpO₂. In 2 studies, greater incidences of occult hypoxemia were observed in patients who were Black, Hispanic, or Asian than in patients who were White. In 1 of these studies, occult hypoxemia was associated with more organ dysfunction and hospital mortality.

A 5-hospital registry study of patients evaluated in the emergency department or hospitalized for COVID-19 found that 24% were not identified as eligible for treatment due to overestimation of SaO₂. The majority of patients (55%) who were not identified as eligible were Black. The study also examined the amount of time delay patients experienced before their treatment eligibility was identified. The median delay for patients who were Black was 1 hour longer than for those who were White.

In pulse oximetry, skin tone is an important variable, but accurately measuring oxygen saturation is a complex process. One observational study in adults was unable to identify a consistently predictable difference between SaO₂ and SpO₂ over time for individual patients. Factors other than skin pigmentation (e.g., peripheral perfusion, pulse oximeter sensor placement) are likely involved.

Despite the limitations of pulse oximetry, an FDA-cleared pulse oximeter for home use can contribute to an assessment of a patient’s overall clinical status. Practitioners should advise patients to follow the manufacturer’s instructions for use, place the oximeter on the index or ring finger, and ensure the hand Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 10/18/2022
is warm, relaxed, and held below the level of the heart. Fingernail polish should be removed before testing. Patients should be at rest, indoors, and breathing quietly without talking for several minutes before testing. Rather than accepting the first reading, patients or caretakers should observe the readings on the pulse oximeter for ≥30 seconds until a steady number is displayed.\textsuperscript{10,15} Patients should inform their health care provider if the reading is repeatedly below a previously specified value (generally 95% on room air at sea level). Pulse oximetry has been widely adopted as a remote patient monitoring tool, but when the use of pulse oximeters is compared with close monitoring of clinical progress via video consultation, telephone calls, text messaging, or home visits, there is insufficient evidence that it improves clinical outcomes.\textsuperscript{16,17}

Not all commercially available pulse oximeters have been cleared by the FDA. SpO\textsubscript{2} readings obtained through non-FDA-cleared devices, such as over-the-counter sports oximeters or mobile phone applications, lack sufficient accuracy for clinical use. Abnormal readings on these devices should be confirmed with an FDA-cleared device or an arterial blood gas analysis.\textsuperscript{18,19}

Regardless of the setting, SpO\textsubscript{2} should always be interpreted within the context of a patient’s entire clinical presentation. A patient’s signs and symptoms (e.g., dyspnea, tachypnea, chest pain, changes in cognition or attentional state, cyanosis) should be given greater weight than a pulse oximetry result.

**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 consistent with COVID-19 pneumonia.\textsuperscript{20,21}

**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 patients who are mildly ill 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 Nonhospitalized Adults With COVID-19](https://www.covid19treatmentguidelines.nih.gov/) for recommendations regarding anti-SARS-CoV-2 therapies.

**Moderate Illness**

Moderate illness is defined as evidence of lower respiratory disease during clinical assessment or imaging, with SpO\textsubscript{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. See [Therapeutic Management of Nonhospitalized Adults With COVID-19](https://www.covid19treatmentguidelines.nih.gov/) for recommendations regarding anti-SARS-CoV-2 therapies. If bacterial pneumonia is suspected, administer empiric antibiotic treatment, re-evaluate the patient daily, and de-escalate or stop antibiotics if further testing indicates the patient does not have a bacterial infection.

**Severe Illness**

Patients with COVID-19 are considered to have severe illness if they have SpO\textsubscript{2} <94% on room air.
at sea level, PaO$_2$/FiO$_2$ <300 mm Hg, a respiratory rate >30 breaths/min, 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 Hospitalized Adults With COVID-19 for recommendations regarding anti-SARS-CoV-2 therapies. If bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate the patient daily, and de-escalate or stop antibiotics if further testing indicates the patient does not have a bacterial infection.

**Critical Illness**

SARS-CoV-2 infection can cause acute respiratory distress syndrome, virus-induced distributive (septic) shock, cardiac shock, an exaggerated inflammatory response, thrombotic disease, and exacerbation of underlying comorbidities.

Successful clinical management of a patient with COVID-19, as with any patient in the intensive care unit (ICU), includes treating both the medical condition that initially resulted in ICU admission as well as other comorbidities and nosocomial complications. For more information, see Critical Care for Adults.

**Infectious Complications in Patients With COVID-19**

Some patients with COVID-19 may have additional infections when they present for care or that develop during the course of treatment. These coinfections may complicate treatment and recovery. Older patients or those with certain comorbidities or immunocompromising conditions may be at higher risk for these infections. The use of immunomodulators such as dexamethasone, interleukin-6 inhibitors (e.g., tocilizumab, sarilumab), or Janus kinase inhibitors (e.g., baricitinib, tofacitinib) to treat COVID-19 may also be a risk factor for infectious complications; however, when these therapies are used appropriately, the benefits outweigh the risks.

Infectious complications in patients with COVID-19 can be categorized as follows:

- **Coinfections at presentation:** Although most individuals present with only SARS-CoV-2 infection, concomitant viral infections, including influenza and other respiratory viruses, have been reported. Community-acquired bacterial pneumonia has also been reported, but it is uncommon, with a prevalence that ranges from 0% to 6% of people with SARS-CoV-2 infection. Antibacterial therapy is generally not recommended unless additional evidence for bacterial pneumonia is present (e.g., leukocytosis, the presence of a focal infiltrate on imaging).

- **Reactivation of latent infections:** There are case reports of underlying chronic hepatitis B virus and latent tuberculosis infections reactivating in patients with COVID-19 who receive immunomodulators as treatment, although the data are currently limited. Reactivation of herpes simplex virus and varicella zoster virus infections have also been reported. Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids. Many clinicians would initiate empiric treatment (e.g., with the antiparasitic drug ivermectin), with or without serologic testing, in patients who are from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).

- **Nosocomial infections:** Hospitalized patients with COVID-19 may acquire common nosocomial infections, such as hospital-acquired pneumonia (including ventilator-associated pneumonia), line-related bacteremia or fungemia, catheter-associated urinary tract infection, and *Clostridioides difficile*–associated diarrhea. Early diagnosis and treatment of these infections are important for improving outcomes in these patients.
• **Opportunistic fungal infections:** Invasive fungal infections, including aspergillosis and mucormycosis, have been reported in hospitalized patients with COVID-19.\(^{31-34}\) Although these infections are relatively rare, they can be fatal, and they may be seen more commonly in patients who are immunocompromised or receiving mechanical ventilation. The majority of mucormycosis cases have been reported in India and are associated with diabetes mellitus or the use of corticosteroids.\(^{35,36}\) The approach for managing these fungal infections should be the same as the approach for managing invasive fungal infections in other settings.

### SARS-CoV-2 Reinfection and Breakthrough Infection

As seen with other viral infections, reinfection after recovery from prior infection has been reported for SARS-CoV-2.\(^ {37}\) Reinfection may occur as initial immune responses to the primary infection wane over time. The true prevalence of reinfection is not known and likely varies depending on the circulating variants. A national database study in Qatar estimated that previous infection prevented reinfection with the Alpha, Beta, and Delta variants of concern (VOCs), with 90%, 86%, and 92% effectiveness, respectively. Protection against reinfection with the Omicron VOC was about 56% effective.\(^ {38}\) Furthermore, an investigation of Omicron infection after Delta infection in 4 U.S. states identified 10 cases of reinfection that occurred <90 days after a symptomatic infection (1 reinfection required hospitalization).\(^ {39}\) The majority of reinfection cases (70%) occurred in people who were unvaccinated. Fewer patients were symptomatic during reinfection than during the initial infection. Among patients who were symptomatic, the median duration of symptoms was shorter with reinfection than with the initial infection.

Breakthrough SARS-CoV-2 infections (i.e., infection in people who completed the primary vaccine series) have been reported.\(^ {40}\) Breakthrough SARS-CoV-2 infection appears to be less likely to lead to severe illness than infection in people who are unvaccinated. An analysis of electronic health record data from a large U.S. sample of 664,722 patients seen from December 2020 to September 2021 found that full vaccination was associated with a 28% reduction in the risk of a breakthrough infection.\(^ {40}\) That study also found that the time to breakthrough infection was shorter for patients with immunocompromising conditions (i.e., people with HIV or solid organ or bone marrow transplant recipients) than for those with no immunocompromising conditions. For information on diagnostic testing in the setting of suspected reinfection, see [Testing for SARS-CoV-2 Infection](#). In addition, [guidelines for the diagnosis and evaluation](#) of suspected SARS-CoV-2 reinfection or breakthrough infection are provided by the Centers for Disease Control and Prevention (CDC).

Although data are limited, no evidence suggests that the treatment of suspected or documented SARS-CoV-2 reinfection or breakthrough infection should be different from the treatment used during the initial infection, as outlined in [Therapeutic Management of Nonhospitalized Adults With COVID-19](#) and [Therapeutic Management of Hospitalized Adults With COVID-19](#).

### Persistent Symptoms and Other Conditions After Acute COVID-19

Some patients may experience persistent symptoms or other conditions after acute COVID-19. Adult and pediatric data on the incidence, natural history, and etiology of these symptoms and organ dysfunction are emerging. However, reports on these data have several limitations, including differing case definitions. In addition, many reports only included patients who attended post-COVID clinics, and the studies often lack comparator groups. No specific treatments for persistent effects of COVID-19 have been shown to be effective, although general management strategies have been proposed, including interim guidance from the CDC, the American Academy of Physical Medicine and Rehabilitation, and the United Kingdom’s COVID-19 rapid guideline.
The nomenclature for this phenomenon is evolving, and no clinical terminology has been established. It has been referred to as post-COVID condition, post-COVID syndrome, post-acute sequelae of SARS-CoV-2, or, colloquially, “long COVID.” Affected patients have been referred to as “long haulers.” MIS-C and multisystem inflammatory syndrome in adults (MIS-A) are serious postinfectious complications of acute COVID-19. For more information on these syndromes, see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

The CDC has defined post-COVID conditions as new, returning, or ongoing symptoms that people experience ≥4 weeks after being infected with SARS-CoV-2. In October 2021, the World Health Organization published a clinical case definition that described the post-COVID clinical condition as usually occurring 3 months after the onset of COVID-19 with symptoms that last for ≥2 months and cannot be explained by an alternative diagnosis.

**Persistent Symptoms**

The prevalence of persistent post-COVID clinical signs and symptoms remains unclear. In a systematic review of 25 observational cohort studies, prevalence varied widely (from 5% to 80%) and likely reflected differences in study populations, case definitions, and data resources. Another large, systematic review found a similar prevalence of post-COVID symptoms 6 months after initial infection between studies from high-income or low- and middle-income countries and between studies in which >60% or <60% of the patients were hospitalized.

A prospective study conducted at the University of Washington investigated mostly outpatients with laboratory-confirmed SARS-CoV-2 infection (150 participants had mild illness, 11 had no symptoms, and 11 had moderate or severe disease that required hospitalization). Participants completed a follow-up questionnaire 3 months to 9 months after illness onset; 33% of outpatients and 31% of hospitalized patients reported ≥1 persistent symptom. Persistent symptoms were reported by 27% of the patients aged 18 to 39 years, 30% of those aged 40 to 64 years, and 43% of those aged ≥65 years.

In these and other studies, the most commonly reported nonneurologic, persistent symptoms included fatigue or muscle weakness, joint pain, chest pain, palpitations, shortness of breath, and cough. From January 2020 to April 2021, the CDC conducted an internet-based survey of 3,135 noninstitutionalized adults who self-reported receiving either a positive or negative SARS-CoV-2 test result. The study found that fatigue, shortness of breath, and cough were commonly reported symptoms lasting >4 weeks after onset. The prevalence of these symptoms among participants with a positive test result versus the prevalence among participants with a negative test result was 22.5% versus 12% for fatigue, 15.5% versus 5.2% for shortness of breath, and 14.5% versus 4.9% for cough.

Some of the reported symptoms overlap with post-intensive care syndrome symptoms that have been described for patients without COVID-19. Prolonged symptoms and disabilities after COVID-19 have also been reported in patients with milder illness, including outpatients.

Patients who had breakthrough infection after COVID-19 vaccination are less likely to report symptoms that persist ≥28 days than patients with SARS-CoV-2 infection who are unvaccinated. The COVID Symptom Study, conducted from December 2020 to July 2021, included participants who used a mobile application to report symptoms after breakthrough infections or reinfection. The investigators found that the odds of reporting symptoms for ≥28 days was reduced by about half among participants who received 2 vaccine doses, when compared with participants who received 1 or 0 vaccine doses.

A study of electronic health record data from 59 health care organizations, primarily in the United States, compared the records of people who did not receive any vaccine doses with records of people
who received 2 vaccine doses. In the 6 months after infection, those who received 2 vaccine doses had a lower risk for some, but not all, long-COVID outcomes, such as fatigue, muscle weakness, loss of the sense of smell, or hair loss.

**Cardiopulmonary Injury**

A U.S. Department of Veterans Affairs (VA) study of a national health care database compared 153,760 veterans who survived the first 30 days of COVID-19 to contemporary and historical control cohorts that had no evidence of SARS-CoV-2 infection. When compared with the control cohorts, patients with history of COVID-19 had a greater incidence of post-acute cardiovascular outcomes (e.g., cerebrovascular disorder, dysrhythmia, inflammatory heart disease, ischemic heart disease, heart failure, thromboembolic disease) at 12 months.

A prospective study of pulmonary function examined longitudinal data from the adult Copenhagen General Population Study and found that pulmonary function declined faster for the 107 patients with mostly mild COVID-19 than for a matched sample from the general population.

**Neuropsychiatric Impairment**

Neuropsychiatric impairments have been reported among patients who have recovered from acute COVID-19. Reported persistent neurologic symptoms include headaches, vision changes, hearing loss, impaired mobility, numbness in extremities, restless legs syndrome, tremors, memory loss, cognitive impairment, sleep difficulties, concentration problems, mood changes, and loss of smell or taste.

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. However, the study authors did not report when the tests were administered in relation to the diagnosis of COVID-19.

A retrospective cohort study examined the electronic health records of 273,618 patients from 59 health care organizations, primarily in the United States. The study reported that cognitive dysfunction (defined using International Classification of Diseases, Tenth Revision codes) 3 to 6 months after diagnosis was worse for people with COVID-19 than for people with influenza. Other studies have reported high rates of anxiety and depression among patients who evaluated their psychiatric distress using self-report scales. Reports also show that patients aged ≤60 years experienced more psychiatric symptoms than patients aged >60 years.

**Metabolic Perturbations**

There have been reports of new-onset diabetes after COVID-19. A study of a VA national health care database analyzed the records of 181,280 people who survived the first 30 days of COVID-19 and compared them to a contemporary control cohort that had no evidence of SARS-CoV-2 infection. People with a history of COVID-19 had a 40% greater risk of diabetes 12 months after infection than people in the control cohort. A CDC study of people aged <18 years reported that those with a history of COVID-19 had an increased risk of diabetes >30 days after SARS-CoV-2 infection when compared with those with no history of infection.

Research on persistent symptoms and other conditions after COVID-19 is ongoing, including the National Institutes of Health’s RECOVER Initiative, which aims to better characterize the prevalence, characteristics, and pathophysiology of post-acute sequelae of SARS-CoV-2 and inform potential therapeutic strategies.
Considerations in Pregnancy

Minimal data are available on differences or unique characteristics of post-acute sequelae of SARS-CoV-2 among pregnant patients. Persistent symptoms after acute COVID-19 have been reported in pregnant people. In a prospective cohort study of 594 patients (95% of whom were outpatients) with SARS-CoV-2 infection who were pregnant or recently pregnant, 25% had persistent symptoms ≥8 weeks after symptom onset. The most commonly reported persistent symptoms among this cohort were fatigue, shortness of breath, and loss of smell or taste. For pregnant patients and their children, as well as for all patients affected by post-acute sequelae of SARS-CoV-2, more research is needed to understand any unique long-term effects of COVID-19. The RECOVER Initiative plans to enroll and longitudinally follow pregnant patients and their children to better understand any long-term effects of COVID-19.

References


