

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 have no symptoms 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 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) $\geq 94\%$ on room air at sea level.
- *Severe illness:* Individuals who have an $\text{SpO}_2 < 94\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates $> 50\%$.
- *Critical illness:* Individuals who have respiratory failure, septic shock, 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.

The risk of progressing to severe disease increases with age and the number of underlying conditions. Patients aged ≥ 50 years, especially those aged ≥ 65 years, and patients who are immunosuppressed, unvaccinated, or not up to date with COVID-19 vaccinations are at a higher risk of progressing to severe COVID-19.^{1,2} Certain underlying conditions are also associated with a higher risk of severe COVID-19, including 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.³ Health care providers should closely monitor patients who have COVID-19 and any of these conditions until clinical recovery is achieved.

The initial evaluation for patients may include chest imaging (e.g., X-ray, ultrasound or computed tomography scan) and an electrocardiogram, if indicated. 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.⁴⁻⁷

The definitions for the severity of illness categories also apply to pregnant patients. However, the threshold for certain interventions is different for pregnant 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.⁸

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.⁹ D-dimer and CRP levels also increase during pregnancy and are often higher in pregnant patients than in nonpregnant patients.¹⁰ Detailed information on treating COVID-19 in pregnant patients can be found in [Special Considerations During Pregnancy and After Delivery](#) and in the pregnancy considerations subsections in the Guidelines.

In children with COVID-19, 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).^{11,12} 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.¹³ 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%. Studies that compared SpO₂ and SaO₂ levels measured before the pandemic found that pulse oximeters overestimated oxygen saturation in people who were classified as having darker skin pigmentation and in people whose race or ethnic origin was reported as non-Hispanic Black, Black, or African American.^{14,15}

Several published reports have compared SpO₂ and SaO₂ measurements in patients with COVID-19, including children.^{14,16-18} The studies demonstrated that occult hypoxemia (defined as an SaO₂ <88% despite an 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 1 of these studies, occult hypoxemia was associated with more organ dysfunction and hospital mortality.¹⁷ These studies did not specify the specific devices used to assess SpO₂ levels. The FDA has recognized the need for better real-world evidence to address ongoing concerns about the accuracy of pulse oximeters when they are used to measure oxygen saturation in people with darker skin pigmentation.¹⁹

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 SaO₂.²⁰ 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 being identified as eligible for treatment. The median delay for patients who were Black was 1 hour longer than the delay for patients 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.¹⁶ 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 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 and inform their health care provider if the reading is repeatedly below a previously specified value (generally 95% on room air at sea level).^{13,21} 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.^{22,23}

Not all commercially available pulse oximeters have been cleared by the FDA. SpO₂ readings obtained through devices not cleared by the FDA, 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.^{24,25}

Regardless of the setting, SpO₂ should always be interpreted within the context of a patient's entire clinical presentation. Regardless of a pulse oximeter reading, a patient's signs and symptoms (e.g., dyspnea, tachypnea, chest pain, changes in cognition or attentional state, cyanosis) should be evaluated.

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. The percentage of individuals who present with asymptomatic infection and progress to clinical disease is unclear. Some asymptomatic individuals have been reported to have objective radiographic findings consistent with COVID-19 pneumonia.^{26,27}

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. No imaging or specific laboratory evaluations are routinely indicated in otherwise healthy patients with mild COVID-19. Patients aged ≥ 50 years, especially those aged ≥ 65 years, patients with certain underlying comorbidities, and patients who are immunosuppressed, unvaccinated, or not up to date with COVID-19 vaccinations are at [higher risk of disease progression](#) and are candidates for antiviral therapy.^{1,2} See [Therapeutic Management of Nonhospitalized Adults With COVID-19](#) 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 an SpO₂ $\geq 94\%$ 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](#) for recommendations regarding

anti-SARS-CoV-2 therapies in patients at high risk of progression to severe disease.

Severe Illness

Patients with COVID-19 are considered to have severe illness if they have an SpO₂ <94% on room air at sea level, PaO₂/FiO₂ <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%. These patients may experience rapid clinical deterioration and should be given oxygen therapy and hospitalized. See [Therapeutic Management of Hospitalized Adults With COVID-19](#) for treatment recommendations.

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.

The clinical management of patients with COVID-19 who are in the intensive care unit should include treatment with immunomodulators and, in some cases, the addition of remdesivir. These patients should also receive treatment for any comorbid conditions and nosocomial complications. For more information, see [Critical Care for Adults](#) and [Therapeutic Management of Hospitalized Adults With COVID-19](#).

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, Janus kinase inhibitors (e.g., baricitinib, tofacitinib), interleukin-6 inhibitors (e.g., tocilizumab, sarilumab), tumor necrosis factor inhibitors (e.g., infliximab), or abatacept to treat COVID-19 may also increase the risk of 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.²⁸⁻³⁰ Community-acquired bacterial pneumonia has also been reported, but it is uncommon.^{28,31,32} 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.³³⁻³⁵ Reactivation of herpes simplex virus and varicella zoster virus infections have also been reported.³⁶ Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.^{37,38} Many clinicians would initiate empiric treatment (e.g., with the antiparasitic drug ivermectin), with or without serologic testing, in patients who require immunomodulators for the treatment of COVID-19 and have come from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).^{39,40}
- *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 diarrhea associated with *Clostridioides difficile*.^{41,42} 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-19.⁴³⁻⁴⁶ 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.^{47,48} 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 respiratory viral infections, reinfection after recovery from prior infection has been reported for SARS-CoV-2.⁴⁹ Reinfection may occur as initial immune responses to the primary infection wane over time. Data regarding the prevalence, risk factors, timing, and severity of reinfection are evolving and vary depending on the circulating variants. Breakthrough SARS-CoV-2 infections (i.e., infection in people who are up to date with COVID-19 vaccinations) also occur.⁵⁰ When compared with infection in people who are unvaccinated, breakthrough infections in vaccinated individuals appear less likely to lead to severe illness or symptoms that persist ≥ 28 days.⁵⁰⁻⁵³ The time to breakthrough infection has been reported to be shorter for patients with immunocompromising conditions (i.e., solid organ or bone marrow transplant recipients or people with HIV) than for those with no immunocompromising conditions.⁵⁰

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](#).

Prolonged Viral Shedding, Persistent Symptoms, and Other Conditions After SARS-CoV-2 Infection

Symptomatic SARS-CoV-2 infection is typically associated with a decline in viral shedding and resolution of COVID-19 symptoms over days to weeks. However, in some cases, reduced viral shedding and symptom resolution are followed by viral or symptom rebound. People who are immunocompromised may experience viral shedding for many weeks. Some people experience symptoms that develop or persist for more than 4 weeks after the initial COVID-19 diagnosis.

Viral or Symptom Rebound Soon After COVID-19

Observational studies and results from clinical trials of therapeutic agents have described SARS-CoV-2 viral or COVID-19 symptom rebound in patients who have completed treatment for COVID-19.⁵⁴⁻⁵⁶ Viral and symptom rebounds have also occurred when anti-SARS-CoV-2 therapies were not used.^{56,57} Typically, this phenomenon has not been associated with progression to severe COVID-19.

Prolonged Viral Shedding in Patients Who Are Immunocompromised

Patients who are immunocompromised may experience prolonged shedding of SARS-CoV-2 with or without COVID-19 symptoms.^{58,59} Prolonged viral shedding may affect SARS-CoV-2 testing strategies and isolation duration for these patients. In some cases, the prolonged shedding may be associated with persistent COVID-19 symptoms. See [Special Considerations in People Who Are Immunocompromised](#) for more information on the clinical management of people who are immunocompromised.

Persistent, New, or Recurrent Symptoms More Than 4 Weeks After SARS-CoV-2 Infection

Some patients report persistent, new, or recurrent symptoms and conditions (e.g., cardiopulmonary injury, neurocognitive impairment, new-onset diabetes, gastrointestinal and dermatologic manifestations) more than 4 weeks after the initial COVID-19 diagnosis.⁶⁰ The nomenclature for this phenomenon is evolving; no clinical terminology has been established. The terminology used includes long COVID, post-COVID condition, post-COVID-19 syndrome, and post-acute sequelae of SARS-CoV-2. Patients who have these symptoms or conditions have been called “long haulers.”

Data on the incidence, natural history, and etiology of these symptoms are emerging. However, reports on these syndromes have several limitations, such as differing case definitions, a lack of comparator groups, and overlap between the reported symptoms and the symptoms of post-intensive care syndrome that have been described in patients without COVID-19. In addition, many reports only included patients who attended post-COVID clinics. Details on the pathogenesis, clinical presentation, and treatment for these conditions are beyond the scope of these Guidelines. The [Centers for Disease Control and Prevention](#) provides information about the timeframes, presentation of symptoms, and management strategies for post-COVID conditions. Research on the prevalence, characteristics, and pathophysiology of persistent symptoms and conditions after COVID-19 is ongoing, including research through the National Institutes of Health’s [RECOVER Initiative](#), which aims to inform potential therapeutic strategies.

MIS-C and multisystem inflammatory syndrome in adults (MIS-A) are serious postinfectious complications of SARS-CoV-2 infection. For more information on these syndromes, see [Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A](#).

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