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Summary
Coronavirus disease 2019 (COVID-19) is an infectious acute respiratory disease caused by a novel coronavirus. The World Health Organization (WHO) was informed of cases of pneumonia of unknown microbial etiology associated with Wuhan City, Hubei Province, China on 31 December 2019. The WHO later announced that a novel coronavirus had been detected in samples taken from these patients. Since then, the epidemic has escalated and rapidly spread around the world, with the WHO first declaring a public health emergency of international concern on 30 January 2020, and then formally declaring it a pandemic on 11 March 2020. Clinical trials and investigations to learn more about the virus, its origin, how it affects humans, and its management are ongoing. This topic is based on the best evidence currently available, but as this is an evolving situation, evidence is limited in some areas and some recommendations may be based on observational studies and retrospective analyses, as well as randomized controlled trials and guidelines.

Definition
A potentially severe acute respiratory infection caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The clinical presentation is generally that of a respiratory infection with a symptom severity ranging from a mild common cold-like illness, to a severe viral pneumonia leading to acute respiratory distress syndrome that is potentially fatal. Characteristic symptoms include fever, cough, dyspnea, and loss of taste/smell, although some patients may have mild upper respiratory tract symptoms or be asymptomatic. Complications of severe disease include, but are not limited to, multi-organ failure, septic shock, and venous thromboembolism. Symptoms may be persistent and continue for more than 12 weeks in some patients.

Several variants of SARS-CoV-2 have been identified. See the Classification section for more information.
Epidemiology

Over 516 million cases have been reported globally, with approximately 6.25 million deaths according to the World Health Organization. The US has the highest number of reported infections and deaths in the world. India, Brazil, France, and Germany have the highest number of infections after the US. Brazil, India, Russia, and Mexico have the highest number of deaths after the US.


Current detailed data for the US situation is available.


Adults

- In China, 87% of confirmed cases were ages 30 to 79 years and 3% were ages 80 years or older in the first wave of the pandemic. Approximately 51% of patients were male.[23]
- In the UK, the median age of patients was 73 years and males accounted for 60% of admissions in a prospective observational cohort study of more than 20,000 hospitalized patients in the first wave.[24]
- In the US, older patients (ages ≥65 years) accounted for 31% of all cases, 45% of hospitalizations, 53% of intensive care unit admissions, and 80% of deaths in the first wave, with the highest incidence of severe outcomes in patients ages ≥85 years.[25]

Adolescents

- Adolescents appear to have similar susceptibility to infection as adults.[26] However, evidence is conflicting and the detailed relationship between age and susceptibility to infection requires further investigation.[27]
- In the US, hospitalizations in adolescents peaked at 2.1 per 100,000 in early January 2021, declined to 0.6 per 100,000 in March, and rose to 1.3 per 100,000 in April. Among hospitalized adolescents,
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approximately one third required admission to the intensive care unit and 5% required mechanical ventilation. This data was based on 204 adolescents who were likely hospitalized primarily for COVID-19 during January 1 to March 31 2021.[28]

Children

- Evidence suggests that children have a lower susceptibility to infection compared with adults.[26] However, evidence is conflicting and the detailed relationship between age and susceptibility to infection requires further investigation.[27] Emerging data suggests variants may spread more effectively and rapidly among young children, although hospitalization rates decreased.[29]
- Most cases in children are from familial clusters, or children who have a history of close contact with an infected patient. It is rare for children to be the index case in household transmission clusters.[30] Unlike adults, children do not seem to be at higher risk for severe illness based on age or sex.[31]
- In the UK, a prospective observational cohort study found that children and young adults represented 0.9% of all hospitalized patients at the time. The median age of children admitted to hospital was 4.6 years, 56% were male, 35% were under 12 months of age, and 42% had at least one comorbidity. In terms of ethnicity, 57% were White, 12% were South Asian, and 10% were Black. Age under 1 month, age 10 to 14 years, and Black race were risk factors for admission to critical care.[32]
- In the US, a retrospective cohort study of over 135,000 children found that the mean age of infected children was 8.8 years, and 53% were male. In terms of ethnicity, 59% were White, 15% were Black, 11% were Hispanic, and 3% were Asian. Only 4% of children tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in this population, and clinical manifestations were typically mild.[33]
- Globally, the case fatality rate in children appears to be higher in low- and middle-income countries compared with high-income countries.[34]

Pregnant women

- The overall prevalence in pregnant and recently pregnant women attending or admitted to hospital for any reason has been estimated to be 10%; however, the rate varies across studies and countries.[35][36] A meta-analysis of over 2500 pregnant women with confirmed disease found that 73.9% of women were in the third trimester; 50.8% were from Black, Asian, or minority ethnic groups; 38.2% were obese; and 32.5% had chronic comorbidities.[37]
- In the UK, the estimated incidence of admission to hospital with confirmed infection in pregnancy is 4.9 per 1000 maternities. Most women were in the second or third trimester. Of these patients, 41% were ages 35 years or older, 56% were from Black or other ethnic minority groups, 69% were overweight or obese, and 34% had preexisting comorbidities.[38]
- In the US, approximately 205,000 cases have been reported in pregnant women (as of 2 May 2022), with over 32,000 hospitalizations and 292 deaths.[39] According to an analysis of approximately 400,000 women ages 15 to 44 years with symptomatic disease, Hispanic and non-Hispanic Black pregnant women appear to be disproportionately affected during pregnancy.[40]

Healthcare workers

- Approximately 14% of the cases reported to the World Health Organization are in healthcare workers (range 2% to 35%).[41]
- The incidence of infection in healthcare workers ranged from 0% to 49.6% (by polymerase chain reaction), and the prevalence of SARS-CoV-2 seropositivity ranged from 1.6% to 31.6%. The wide ranges are likely related to differences in settings, exposures, rates of community transmission,
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There was no consistent association between sex, age, or healthcare worker role (i.e., nurse versus physician) and risk for infection or seropositivity. However, non-White race (Black, Asian or Asian/Pacific Islander, or combined non-White races) or Hispanic ethnicity was significantly associated with an increased risk of infection compared with White people. Working in a hospital unit with COVID-19 patients, being a frontline worker, and direct or prolonged patient contact were also associated with an increased risk for infection. Household or private setting exposure was a stronger risk factor than work exposure in most studies. The presence of immunoglobulin G antibodies was associated with a decreased risk for reinfection.[42] [43]

Etiology

Virology

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown betacoronavirus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019.[44]
- Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), and others that circulate among mammals and birds. Rarely, animal coronaviruses can spread to humans and subsequently spread between people, as was the case with SARS and MERS.
- SARS-CoV-2 belongs to the Sarbecovirus subgenus of the Coronaviridae family, and is the seventh coronavirus known to infect humans. The virus has been found to be similar to SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV.[45] [46]
- See the Classification section for information on SARS-CoV-2 variants.
Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically

Centers for Disease Control and Prevention

Origin of virus

- A majority of patients in the initial stages of this outbreak reported a link to the Huanan South China Seafood Market, a live animal or "wet" market, suggesting a zoonotic origin of the virus.[47] [48] [49] An initial assessment of the transmission dynamics in the first 425 confirmed cases found that 55% of cases before 1 January 2020 were linked to the market, whereas only 8.6% of cases after this date were linked to the market. This suggests that person-to-person spread was occurring among close contacts since the middle of December 2019.[49] More recent studies suggest that the virus may have emerged earlier than previously thought.[50]
- A zoonotic origin has still not been confirmed. Some studies suggest that SARS-CoV-2 may be a recombinant virus between a bat coronavirus and an origin-unknown coronavirus, with pangolins and minks suggested as possible intermediate hosts. However, there is currently no evidence to demonstrate the possible route of transmission from a bat reservoir to human through one or several intermediary animal species.[51] Further research is required to determine the origin of SARS-CoV-2.

Transmission dynamics

- Respiratory transmission is the dominant mode of transmission, with proximity and ventilation being the key determinants of transmission risk.[52] Available evidence suggests that transmission between people occurs primarily when an infected person is in close contact with another person. The virus can spread from an infected person's mouth or nose in small liquid particles (ranging in size from larger droplets to smaller aerosols) when the person coughs, sneezes, sings, breathes heavily, or talks. Close-range contact can result in inhalation of, or inoculation with, the virus through the mouth, nose, or eyes.[53]
- Aerosol transmission can occur in healthcare settings during aerosol-generating procedures. There are also some outbreak reports that suggest aerosol transmission is possible in the community.
under certain conditions; however, these reports relate to enclosed indoor crowded spaces with poor ventilation where the infected person may have been breathing heavily (e.g., restaurants, choir practice, fitness classes). A detailed investigation of these clusters suggests that droplet and fomite transmission could also explain the transmission in these reports.[53] While the air close to, and distant from, patients has been found to frequently be contaminated with SARS-CoV-2 RNA, few of these samples contained viable virus.[54] The risk of transmission is much lower outdoors compared with indoors, with a limited number of studies estimating a transmission rate of <1%. [55] Evidence that nebulizer treatments increase the risk of transmission of coronaviruses similar to SARS-CoV-2 is inconclusive, and there is minimal direct evidence about the risk for transmission of SARS-CoV-2.[56]

- Fomite transmission (from direct contact with fomites) may be possible, but there is currently no conclusive evidence for this mode of transmission. In the few cases where fomite transmission has been presumed, respiratory transmission has not been completely excluded.[52] While the majority of studies report identification of the virus on inanimate surfaces, there is a lack of evidence to demonstrate recovery of viable virus.[57]

- Fecal-oral transmission (or respiratory transmission through aerosolized feces) may be possible, but there is only limited circumstantial evidence to support this mode of transmission.[52]

- Transmission via other body fluids (including sexual transmission or bloodborne transmission) has not been reported.[52] While the virus has been detected in body fluids (e.g., semen, urine, cerebrospinal fluid, ocular fluids), the presence of virus or viral components does not equate with infectivity.[58]

- Vertical transmission occurs rarely and transplacental transmission has been documented. There is limited evidence on the extent of vertical transmission and its timing.[59] Viral fragments have been detected in breast milk; however, this finding is uncommon and, when it occurs, has been associated with mild symptoms in infants.[60]

- Nosocomial transmission was reported in 44% of patients in one systematic review; however, this review was limited to case series conducted early in the outbreak in Wuhan before the institution of appropriate infection prevention and control measures.[61] Hospital-acquired infections accounted for approximately 11.3% of infections in the UK between February and August 2020. This peaked at 15.8% in the middle of May. Rates as high as 25% were reported in some areas in October 2020. Rates were notably higher in residential community care hospitals (61.9%) and mental health hospitals (67.5%) compared with acute and general care hospitals (9.7%).[62] [63] Studies of healthcare workers exposed to index cases (not in the presence of aerosol-generating procedures) found little to no nosocomial transmission when contact and droplet precautions were used.[64]

- [BMJ: visualising SARS-CoV-2 transmission routes and mitigations] (https://www.bmj.com/content/375/bmj-2021-065312)

### Transmission dynamics in relation to symptoms

- Transmission is more likely if contacts are exposed shortly before or after symptom onset in the index patient. In one study, the risk of transmission to close contacts was higher if exposure occurred between -2 and 3 days from symptom onset in the index patient. Among contacts who became infected, asymptomatic infection was more common if they were exposed to an asymptomatic index patient, suggesting that disease severity in the index patient may be associated with the clinical presentation of disease.[65]

- Symptomatic transmission
  - Transmission mainly occurs via respiratory droplets or aerosols during close contact with an infected symptomatic case. Transmissibility depends on the amount of viable virus being shed
and expelled by a person, the type of contact, the setting, and what infection prevention and control measures are in place.[53]

• Presymptomatic transmission
  • Transmission may occur during the incubation period before symptom onset. Only 7% of people exposed to a presymptomatic index case became infected in one systematic review.[66] People without symptoms may be presymptomatic, or they may remain persistently asymptomatic.

• Asymptomatic transmission
  • Transmission from asymptomatic cases (laboratory-confirmed cases who never develop symptoms) has been reported; however, most of the evidence is based on early data from China and has limitations (e.g., small number of cases, cases may have been presymptomatic).[67] Numerous studies have reported no evidence of asymptomatic transmission from carriers of SARS-CoV-2, including a large study in nearly 10 million residents in Wuhan.[74] [75] [76] [77] Only 1% of people exposed to an asymptomatic index case became infected in one systematic review, suggesting limited infectiousness.[66]
  • Estimating the prevalence of asymptomatic cases in the population is difficult. A meta-analysis of over 130,000 people found that 21.7% remained asymptomatic throughout the course of the infection (after excluding presymptomatic cases). Subgroup analysis showed that the overall rate of asymptomatic infections was higher in pregnant women (48.8%) and children (32.1%). African studies reported the highest asymptomatic infection rate, while Asian studies reported the lowest.[78]
  • Healthcare workers may play a role in asymptomatic transmission. About 7.6% of healthcare workers who worked in hospital units with infected patients tested positive for SARS-CoV-2 antibodies; however, only 58% of these workers reported prior symptoms.[79]
  • Although there is some evidence that older children have higher rates of asymptomatic disease than infants <1 year of age, the majority of children present with symptomatic disease and do not appear to be silent spreaders of infection.[27]

Superspreading events
  • Superspreading events have been reported. These events are associated with explosive growth early in an outbreak and sustained transmission in later stages. Examples include church/religious gatherings, family or social gatherings, choir practices, indoor recreational sporting activities, nightclubs, restaurants, business conferences, and working in call centers. Widespread transmission has also been reported in long-term care facilities, homeless shelters, prisons, and meat and poultry processing facilities, as well as on board cruise ships.[80]
  • Limited transmission has been reported in childcare, school, and university settings.[81] [82] There is limited high-quality evidence to quantify the extent of transmission in schools, or to compare it with community transmission. However, evidence suggests a lower overall infection attack rate in school staff (1.18%) compared with students (1.66%). Emerging evidence suggests the overall infection attack rate and SARS-CoV-2 positivity rate in school settings are low.[83] During periods of low incidence of infection in the local population in schools with nonpharmaceutical interventions in place, the risk to school staff is not generally higher than that of the general population and not comparable to other high-risk professions (e.g., healthcare workers). Studies reporting periods of high incidence of infection are limited, but do show a higher risk to school staff in these circumstances.[84] In one
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study, infection in close contacts in secondary schools and colleges in England was uncommon (approximately 2%).[85]

- Some individuals are supershedders of virus, but the reasons underlying superspreader events are often more complex than just excess virus shedding and can include a variety of behavioral, host, and environmental factors.[86]

Viral transmission factors

- Incubation period

  - The incubation period is estimated to be between 1 and 14 days, with a median of 5 to 7 days (9.6 days in children).[87] [88] [89]

- Reproduction number ($R_0$)

  - A systematic review and analysis estimates the reproduction number to be 2.69 (based on published literature from January to August 2020).[90] The Centers for Disease Control and Prevention estimates the $R_0$ to be 2.5.[91]

- Serial interval

  - The serial interval has been estimated to be approximately 5.45 days (range 4.2 to 6.7 days).[92] Emerging evidence does not support a significant difference in serial interval between the Delta and wild-type variants.[93]

- Secondary attack rate

  - The pooled secondary attack rate among all close contacts of an index case has been estimated to be 7%, based on data from early in the pandemic.[94] The pooled rate varies between contact settings with an estimated rate of 18.9% to 21.1% in household settings (as of 17 June 2021), 3.6% in healthcare facilities, 1.2% to 5.9% in social settings, and 1.9% in workplaces. The rate is higher for symptomatic index cases compared with asymptomatic cases, and adults compared with children.[95] [96] [97] A higher overall secondary attack rate of 37.3% has been reported in household settings in a more recent meta-analysis due to circulating SARS-CoV-2 variants.[98] The overall pooled secondary attack rate in aged-care facilities was much higher: 42% among residents and 22% among staff.[99] The rate in children and young people was higher in household settings compared with school settings.[100] Secondary attack rates for SARS-CoV-2 variants may differ. The secondary attack rate for the Omicron variant is higher compared with other SARS-CoV-2 variants.[98] [101] See the Classification section for more information.

- Viral load

  - Viral load appears to be a leading driver of virus transmission; higher viral loads are associated with increased secondary attack rates and a higher risk of developing symptomatic disease.[102] Viral load is highest in the upper respiratory tract (nasopharynx and oropharynx) early in the course of infection (usually peaks in the first week of illness), and then increases in the lower respiratory tract (sputum). Viral load decreases after symptom onset. Patients with severe disease have higher viral loads compared with those with mild disease. Viral load in the upper respiratory tract is comparable in asymptomatic and symptomatic patients; however,
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most studies demonstrate faster viral clearance among asymptomatic people compared with symptomatic people.[103]

• Viral shedding

  • The mean duration of viral shedding depends on the specimen: 17 days in the upper respiratory tract (maximum 83 days); 14.6 days in the lower respiratory tract (maximum 59 days); and 17.2 days in stool (maximum 126 days). Duration of shedding was longer in symptomatic patients compared with asymptomatic patients, and in patients with severe illness compared with those with nonsevere illness.[103] Immunosuppressed patients may shed for at least 2 months.[104] There is no convincing evidence that duration of viral shedding correlates with duration of infectivity.[105] No viable virus has been isolated in patients with mild or moderate disease after 10 days of symptoms, or after 20 days in those with severe or critical disease, despite ongoing viral shedding.[52]

• Human challenge study

  • The first human challenge study has been published on a preprint server (not peer reviewed). A total of 36 volunteers ages 18 to 29 years without evidence of previous infection or vaccination were inoculated with an intranasal dose of wild-type SARS-CoV-2 virus. Eighteen volunteers (53%) became infected. Most (89%) had either no or mild to moderate symptoms. In those infected, viral shedding became quantifiable in throat swabs from 40 hours. Viral load rose steeply and peaked at 5 days post-inoculation. Virus was first detected in the throat, but rose to significantly higher levels in the nose for up to 10 days post-inoculation.[106]

Pathophysiology

The exact pathophysiology remains unknown, partly due to the scarcity of postmortem studies.[107] The pathophysiology resembles that of other coronavirus infections. However, emerging evidence indicates that COVID-19 has distinctive pathophysiological features that set it apart from respiratory failure of other origins.[108]

SARS-CoV-2 attaches to the angiotensin-converting enzyme-2 (ACE2) receptor on target host cells, followed by internalization and replication of the virus. ACE2 receptors are highly expressed in the upper and lower respiratory tract cells, but are also expressed in myocardial cells, renal epithelial cells, enterocytes, and endothelial cells in multiple organs, which may explain the extrapulmonary manifestations associated with the disease.[109] Viral RNA has been identified in many organs in postmortem studies.[107]
Multi-organ complications of COVID-19 and long COVID. The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor

BMJ. 2021;374:n1648

The virus uses host transmembrane protease serine 2 (TMPRSS2) for viral spike protein priming and fusion of viral and host cell membranes.[110] The SARS-CoV-2 spike protein plays a key role in the recognition of the ACE2 receptor and cell membrane fusion process. A unique structural feature of the spike glycoprotein receptor-binding domain confers potentially higher binding affinity for ACE2 on host cells compared with SARS-CoV-1.[111] This furin-like cleavage site does not appear to exist in other coronaviruses.[112] The binding energy between the spike protein and ACE2 was highest for humans out of all species tested in one study, suggesting that the spike protein is uniquely evolved to bind to and infect human cells expressing ACE2.[113] Emerging evidence suggests that the spike protein alone may damage endothelial cells by downregulating ACE2 and consequently inhibiting mitochondrial function. Further research is required on whether the spike protein can by itself trigger cell signaling that could lead to various biologic processes.[114] SARS-CoV-2 variants may be more transmissible, at least in part, due to enhanced spike protein binding affinity for the ACE2 receptor.[115]
In addition to direct cytopathic viral injury, severe disease is frequently complicated by an infection-induced microangiopathy or hypercoagulable state that causes capillary, venous, and/or arterial thrombosis, which may lead to end-organ damage due to distant thrombotic or embolic disease. Widespread microthrombi have been identified in almost every organ in postmortem studies. The predominant pathologic findings in fatal cases were diffuse alveolar damage, coagulopathy, and hemodynamic compromise. Involvement of nonpulmonary organs was limited to mild parenchymal inflammation (e.g., myocarditis, hepatitis, encephalitis). Direct viral cytopathic injury of extrapulmonary organs in general was not regarded as the cause of organ failure. [109] [107] Three major tissue phenotypes have emerged in postmortem lung tissue: a classic phenotype characterized by progressive diffuse alveolar damage; bronchopneumonia from secondary infection; and tissue thrombosis. These phenotypes are not mutually exclusive and may overlap. [117] SARS-CoV-2-induced endotheliitis may play a role in both the respiratory and nonrespiratory manifestations. [118]

SARS-CoV-2 placentitis is a distinct pathologic entity that has been reported in pregnant women, and is characterized by massive perivillous fibrin deposition and chronic histiocytic intervillositis. It is associated with increased risk of pregnancy loss. [119]

Genetic factors may play a role in susceptibility to infection and disease severity; however, further research is required. [120] [121] [122] [123]
Classification

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant classification

All viruses, including SARS-CoV-2, change over time. Most changes have little to no impact on the virus' properties; however, some changes may affect virus transmission, disease severity, and performance of diagnostic tests, therapeutics, or vaccines.

These variants have been emerging and circulating around the world since the beginning of the pandemic, and are routinely monitored and classified as either variants under monitoring, variants of interest, or variants of concern by the World Health Organization (WHO).[2] These classification systems may vary between countries. For example, in the UK, variants are only classified as variants of concern by the UK Health Security Agency (UKHSA). The classifications of variants in monitoring and variants under investigation were used previously but have since been retired.[3] In the US, variants are classified by the Centers for Disease Control and Prevention (CDC) as variants being monitored, variants of interest, variants of concern, or variants of high consequence.[4]

The WHO has assigned simple labels for key variants using letters of the Greek alphabet. This does not replace existing scientific names (e.g., Pango, Nextstrain, GISAID), which continue to be used in research.[2]

Variant of interest

- The WHO defines a variant of interest as a variant with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, or diagnostic or therapeutic escape; and that has been identified to cause significant community transmission or multiple case clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiologic impacts to suggest an emerging risk to global public health.[2]
- There are currently no circulating variants of interest, according to the WHO and the CDC. Previously circulating variants of interest include the Epsilon, Zeta, Eta, Theta, Iota, Kappa, Lambda, and Mu variants.[2] [4]

Variant of concern

- The WHO defines a variant of concern as a variant that has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:[2]
  - Increase in transmissibility or detrimental change in epidemiology
  - Increased virulence or change in clinical disease presentation
  - Decrease in effectiveness of public health and social measures, or available diagnostics, therapeutics, or vaccines.
- Current variants of concern according to the WHO and the CDC are the Delta and Omicron variants. Previously circulating variants of concern include the Alpha, Beta, and Gamma variants.[2] [4]

Alpha variant

The Alpha variant was previously classified as a variant of concern.[2] [3] [4]
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• Pango lineage: B.1.1.7.
• Earliest documented samples: UK (September 2020).
• Transmissibility: appears greater than the wild type virus.[3]
• Disease severity: appears to be associated with an increased risk of hospitalization and intensive care unit admission (suggesting more severe disease), but not mortality, compared with the wild-type virus, although data are conflicting. Not associated with changes in the symptoms reported or their duration.[5] [6] [7] [8]

Beta variant

The Beta variant was previously classified as a variant of concern.[2] [3] [4]

• Pango lineage: B.1.351.
• Earliest documented samples: South Africa (May 2020).
• Transmissibility: no more transmissible than Alpha.[3]
• Disease severity: insufficient information available.[3]

Gamma variant

The Gamma variant was previously classified as a variant of concern.[2] [3] [4]

• Pango lineage: P.1.
• Earliest documented samples: Brazil (November 2020).
• Transmissibility: appears greater than the wild type virus.[3]
• Disease severity: insufficient information available.[3]

Delta variant

The Delta variant is currently classified as a variant of concern by the WHO, but is no longer classified as a variant of concern by the UKHSA and the CDC.[2] [3] [4]

• Pango lineage: B.1.617.2 (including all AY sublineages).
• Earliest documented samples: India (October 2020).
• Transmissibility: appears greater than the wild type virus and Alpha. In the UK, the secondary attack rate among household contacts of cases that have not traveled was 11.3% (12.3% for the AY.4.2 sublineage based on limited data), compared with 10.2% with Alpha (as of 22 November 2021).[3]
• Disease severity: appears to be associated with an increased risk of hospitalization (suggesting more severe disease) compared with contemporaneous Alpha cases; however, there is a high level of uncertainty in these findings. The crude case fatality rate is estimated to be 0.53%, considerably less than the Alpha variant (as of 26 October 2021). There is no evidence that the AY.4.2 sublineage causes more severe disease than other Delta variants.[3] Observational evidence suggests that infection with Delta was associated with more severe disease compared with Beta.[9]

Omicron variant

The Omicron variant (Pango lineage B.1.1.529) is currently classified as a variant of concern by the WHO, the UKHSA, and the CDC.[2] [3] [4] Omicron is a highly divergent variant with a high number of mutations. There is no path of transmission linking Omicron to its predecessors (Alpha, Delta), and it has been
estimated that its closest-known genetic ancestor likely dates back to some time after mid-2020. Cases were first reported in South Africa in November 2021. The Omicron variant has become the dominant variant in many countries.

The Omicron variant comprises several known lineages including the parental lineage B.1.1.529, and the descendant sublineages (or subvariants) BA.1, BA.1.1, BA.2, BA.3, BA.4, and BA.5. The BA.2 lineage has become the dominant subvariant in some countries, while the incidence of BA.4 and BA.5 lineages is currently increasing in some countries.

Transmissibility

- Omicron has substantial growth advantage over Delta, and has rapidly replaced Delta globally. There is significant evidence that immune evasion contributes to its rapid spread, but it is unknown how much intrinsic increased transmissibility contributes and further research is required. The growth of the BA.2 lineage is increasing in some countries, but it is currently unclear what the drivers of transmission are. Although data suggest that BA.2 is more transmissible than BA.1, the difference in transmissibility appears to be much smaller than the difference between BA.1 and Delta. BA.2 has demonstrated an increased growth rate compared with BA.1. There is preliminary evidence from South Africa that the BA.4 and BA.5 lineages have a growth advantage compared with BA.2.
- In the UK, the secondary attack rate was 11.4% for lineage BA.1 among household contacts (14.3% for lineage BA.2), and 4.6% for lineage BA.1 in nonhousehold contacts (6.1% for lineage BA.2) as of 21 February 2022. These rates decrease over time as more data is accumulated. Secondary attack rates for Alpha and Delta were 10.2% and 11.3% (see above).

Disease severity

- Data from South Africa, the UK, Canada, and Denmark suggest a reduced risk of hospitalization for Omicron compared with Delta. Epidemiologic trends continue to show a decoupling between cases and hospital admissions and deaths compared with previous variants, likely due to a lower intrinsic severity of the variant and preserved vaccine efficacy against severe disease.
- Data from the US also supports this trend, but acknowledges that a higher number of cases (5 times higher than the Delta wave) due to increased transmissibility of the variant is resulting in a record number of hospitalizations (1.8 times higher compared with the Delta wave).
- Observational data from long-term care facilities in England found that the risk of hospitalization and death was lower during the Omicron period compared with the pre-Omicron period.
- Evidence from animal studies suggests that Omicron does not infect cells deep in the lung as readily as it does cells in the upper airways.
- There is no reported difference in severity or hospitalization between BA.2 and BA.1. There is insufficient data to determine whether BA.4 or BA.5 lineages cause more severe disease or an increased risk of hospitalization compared with BA.1 or BA.2.

Vaccine efficacy

- There is growing (not peer reviewed) evidence on vaccine effectiveness for Omicron, with data available from South Africa, the UK, the US, Canada, and Denmark. Early data suggests that the efficacy is significantly lower against Omicron infection and symptomatic disease compared with Delta, with homologous and heterologous booster doses increasing vaccine effectiveness. Vaccine efficacy estimates against severe outcomes (e.g., hospitalization) are lower for Omicron compared with Delta,
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but mostly remain >50% after the primary series and improve with a booster dose to >80%. However, it is uncertain how long this increased protection lasts for.[11]

• Specific vaccines for the Omicron variant are currently in clinical trials, but have not shown promise in animal studies.[16] [17]
• There is no reported difference in vaccine efficacy between BA.2 and BA.1.[3] There is insufficient data to determine whether BA.4 or BA.5 lineages affect vaccine efficacy.[3]

Diagnosis

• The diagnostic accuracy of polymerase chain reaction and rapid antigen tests does not appear to be influenced by the Omicron variant.[11]

Therapeutics

• Treatments for severe or critical disease are expected to remain effective. However, monoclonal antibodies may have decreased neutralization against Omicron based on preliminary preprint (not peer reviewed) data. Monoclonal antibodies will need to be tested individually for their antigen binding and virus neutralization.[11] [18]
• Preclinical evidence suggests that casirivimab/imdevimab and bamlanivimab/etesevimab lack neutralization activity against the Omicron variant in vitro. Sotrovimab and bebtelovimab appear to retain activity against Omicron; however, sotrovimab is not active against the BA.2 subvariant.[19] [20] [21]

Reinfection

• Increased risk of reinfection has been reported by South Africa, the UK, the US, Denmark, and Israel.[11] [22]

Recombinant variants

Several recombinant SARS-CoV-2 variants have been identified over the course of the pandemic, and the vast majority do not confer any advantage to the virus and die out relatively quickly.[3]

Recombinant lineages involving the Omicron variant have been reported. A combination of the BA.1 omicron variant and the Delta variant (also known as BA.1 x AY.4 recombinant, XD and XF, or “deltacron”) is being monitored, but there is currently limited information available. A recombinant of Omicron BA.1 and BA.2 (known as XE) has also been reported.[3]

Resources

The following resources are available:

Case history

Case history #1

A 61-year-old man presents to the hospital with fever, dry cough, and difficulty breathing. He also reports feeling very tired and unwell. He has a history of hypertension, which is controlled with enalapril. On exam, his pulse is 120 bpm, his temperature is 101.6°F (38.7°C), and his oxygen saturation is 88%. He appears acutely ill. He is admitted to hospital in an isolation room and is started on oxygen, intravenous fluids, and venous thromboembolism prophylaxis. Blood and sputum cultures are ordered. Chest x-ray shows bilateral lung infiltrates, and computed tomography of the chest reveals multiple bilateral lobular and subsegmental areas of ground-glass opacity. A nasopharyngeal swab is sent for real-time reverse transcriptase polymerase chain reaction testing, and the result comes back positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) a few hours later.

Case history #2

A 26-year-old woman presents at her local COVID-19 testing clinic with symptoms of a sore throat and loss of taste. She denies having a fever, and has not knowingly been in contact with a confirmed case of COVID-19. After being tested, she is advised to go home, self-isolate until her test results are sent to her via text message, and call her doctor if her symptoms get worse. She receives a text message later that day confirming that her test is positive for SARS-CoV-2, and that she must self-isolate according to her local public health recommendations.

Other presentations

See the Diagnosis section for more information on other presentations.
Approach

Early recognition and rapid diagnosis are essential to prevent transmission and provide supportive care in a timely manner. Have a high index of clinical suspicion for COVID-19 in all patients who present with fever and/or acute respiratory illness; however, be aware that some patients may not present with signs or symptoms of a febrile respiratory illness.

Best Practice has published a separate topic on the Management of coexisting conditions in the context of COVID-19.

Key recommendations

- COVID-19 is a notifiable disease. Report all suspected or confirmed cases to your local health authorities.
- Isolate all suspected or confirmed cases immediately. Triage patients with a standardized triage tool and evaluate the severity of disease. Follow local infection prevention and control guidelines.[87]
- Have a high index of clinical suspicion in all patients who present with fever and/or acute respiratory illness. People with a history of residence/work/travel in a location with a high risk of transmission or community transmission and contacts of probable and confirmed cases are at higher risk of infection.[124]
- Suspect the diagnosis in patients with a new continuous cough, fever, or altered sense of taste or smell. Other common symptoms, particularly in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants and highly vaccinated populations, include headache, sore throat, rhinorrhea, sneezing, and fatigue. Patients may also present with dyspnea, myalgia/arthritis, sputum production, chest tightness, or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).[538]
- Order a real-time reverse transcription polymerase chain reaction (RT-PCR) to confirm the diagnosis. Upper and lower respiratory specimens are preferred. Serologic testing may be useful in some settings.[539] Results should be interpreted in the context of the pretest probability of disease.
- Be on high alert for children and adolescents with acute gastrointestinal symptoms and signs of cardiac inflammation. Evidence so far suggests a milder or asymptomatic course of disease in children and adolescents.[540] However, a rare multisystem inflammatory condition with some features similar to those of Kawasaki disease and toxic shock syndrome has been temporally associated with COVID-19 in children and adolescents.[541]
- Order the following laboratory investigations in hospitalized patients: complete blood count, comprehensive metabolic panel, arterial blood gas, blood glucose level, coagulation screen, inflammatory markers, cardiac biomarkers, serum creatine kinase, and blood and sputum cultures for other pathogens. Pulse oximetry may reveal low oxygen saturation.
- Prioritize a chest x-ray in patients who are seriously ill with suspected pneumonia. Consider a computed tomography (CT) scan of the chest if chest x-ray is uncertain or normal.[542] Consult local guidelines.
- For full details and guidance see information below.

Care pathways

COVID-19 care pathways should be established at local, regional, and national levels for people with suspected or confirmed COVID-19.[87]
• Screen patients at the first point of contact within the health system based on case definitions and an assessment of symptoms, and enter suspected or confirmed cases into the pathway. Suspected cases should remain in the pathway until proven negative.
• Immediately isolate all suspected and confirmed cases and implement local infection prevention and control procedures.
• Triage patients with a standardized triage tool and evaluate the patient to assess the severity of disease.
• Use clinical judgment, including consideration of the patient’s values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the intensive care unit, rather than currently available prediction models for prognosis.

History
Take a detailed history to ascertain the level of risk for COVID-19 and assess the possibility of other causes, including a travel history and an assessment of risk factors.

Suspect the diagnosis in:[124]

• People residing or working in an area with a high risk of transmission (e.g., closed residential settings, humanitarian setting), people residing in or traveling to an area with community transmission, and people working in a health setting (including within health facilities and households) at any time within the 14 days prior to symptom onset
• People who have had contact with a probable or confirmed case. A contact is a person who has experienced any one of the following exposures:
  • Face-to-face contact with a probable or confirmed case within 3 feet (1 meter) and for at least 15 minutes
  • Direct physical contact with a probable or confirmed case
  • Direct care for a patient with probable or confirmed COVID-19 without using recommended personal protective equipment
  • Other situations as indicated by local risk assessments.

Exposure must have occurred during the infectious period of the case. For symptomatic cases, this means 2 days before and 10 days after symptom onset of the case, plus at least 3 additional days without symptoms, for a minimum of 13 days total after symptom onset. For asymptomatic cases, this means 2 days before and 10 days after the date on which the sample that led to confirmation was taken.

The Centers for Disease Control and Prevention defines a close contact as someone who has been within 6 feet (2 meters) of an infected person for at least 15 minutes over a 24-hour period, beginning 2 days before symptom onset (or 2 days before testing in asymptomatic patients).[125]

Clinical presentation in adults
Some patients may be minimally symptomatic or asymptomatic, while others may present with severe pneumonia or complications such as acute respiratory syndrome, septic shock, acute myocardial infarction, venous thromboembolism, or multi-organ failure. Approximately 80% of patients have mild illness that does not warrant medical intervention or hospitalization.[19]

The classic key symptoms are:
Coronavirus disease 2019 (COVID-19)

Diagnosis

- Fever
- Cough
- Dyspnea
- Altered sense of taste/smell.

Other common symptoms, particularly in the context of circulating SARS-CoV-2 variants and highly vaccinated populations, include:

- Headache
- Sore throat
- Rhinorrhea/nasal congestion
- Sneezing
- Fatigue.

Less common or uncommon symptoms include:

- Myalgia or arthralgia
- Sputum production
- Chest tightness/pain
- Gastrointestinal symptoms
- Dizziness
- Neurologic symptoms
- Ocular symptoms
- Audio-vestibular symptoms
- Mucocutaneous symptoms
- Lower urinary tract symptoms
- Hemoptysis.

The UK’s official list of COVID-19 symptoms was updated in April 2022 to include sore throat, fatigue, headache, dyspnea, aching body, blocked or runny nose, loss of appetite, diarrhea, and feeling sick or being sick. Previously, the UK’s official list of symptoms only included fever, persistent cough, and loss or change in taste or smell.[543]

No single sign or symptom can accurately diagnose COVID-19, and neither the absence or presence of specific signs or symptoms are accurate enough to rule in or rule out disease.

- A Cochrane review found that at least half of patients had a cough, sore throat, fever, myalgia/arthralgia, fatigue, or headache. Anosmia and/or ageusia was also common. The presence of fever, myalgia/arthralgia, fatigue, and headache substantially increased the likelihood of COVID-19 when present. Cough and sore throat were common in people without COVID-19, so these symptoms alone were less helpful for diagnosis. The presence of anosmia and/or ageusia may be useful as a red flag for diagnosis. The presence of fever or cough may also be useful to identify people for further testing.[538]
- Nonrespiratory symptoms may appear before the onset of fever and lower respiratory tract symptoms.[544]

Signs and symptoms may differ in the context of circulating SARS-CoV-2 variants or highly vaccinated populations.
• Data from the UK COVID Symptom Study in the context of the Delta variant report that the most common symptoms after full vaccination are headache, rhinorrhea, sneezing, and sore throat. The previous traditional symptoms such as anosmia, shortness of breath, fever, and cough rank further down the list and are no longer top indicators of having COVID-19 in vaccinated people, according to this data. In patients who are unvaccinated, headache, sore throat, rhinorrhea, fever, and persistent cough are the most common symptoms, which differs from when the disease initially appeared.[545]

• Data from the UK COVID Symptom Study in the context of the Omicron variant report that the most common symptoms are headache, runny nose, sneezing, sore throat, and mild to severe fatigue. The initial analysis found no clear differences in early symptoms between Delta and Omicron.[546]

• Symptoms that characterize infection with the Omicron variant differ moderately from those that characterize infection with the Delta variant. Sore throat and hoarse voice were consistently more prevalent among people with Omicron infection compared with those with Delta infection. Loss of/altered smell, eye soreness/burning, sneezing, headache, fever, dizziness, and brain fog were significantly less prevalent among people with Omicron infection compared with those with Delta infection. Loss of smell, a pathognomonic feature of previous SARS-CoV-2 variants, was present in only <20% of cases of people infected with the Omicron variant.[547]

Pregnant women generally present in a similar way to nonpregnant people.

• The clinical characteristics in pregnant women are similar to those reported for nonpregnant adults.[548]

• The most common symptoms in pregnant women are fever and cough. However, pregnant women are less likely to report fever, dyspnea, and myalgia compared with nonpregnant women of reproductive age. Pregnant and recently pregnant women were more likely to be asymptomatic than nonpregnant women of reproductive age.[35] [36]

• It is important to note that symptoms such as fever, dyspnea, gastrointestinal symptoms, and fatigue may overlap with symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events.[87]

Atypical presentations have been reported.

• Atypical presentations may occur, especially in older patients and patients who are immunocompromised (e.g., falls, delirium/confusion, functional decline, reduced mobility, syncope, absence of fever). Older patients and those with comorbidities may present with mild symptoms, but have a high risk of deterioration.[87]

• There have been case reports of parotitis (possibly related to intraparotid lymphadenitis), oral vesiculobullous lesions, retinal lesions, persistent hiccups, and androgenetic alopecia in patients with COVID-19; however, it is unknown whether these findings are associated with SARS-CoV-2 infection as yet.[549] [550] [551] [552] [553]

Coinfections are possible.

• The pooled prevalence of coinfection in SARS-CoV-2-positive patients was 19%, with viral coinfections being more common than bacterial and fungal coinfections. The most frequently identified bacteria were Klebsiella pneumonia, Streptococcus pneumoniae, and Staphylococcus aureus. The most frequently identified viruses were influenza type A, influenza type B, and respiratory syncytial virus. The most frequently identified fungi was Aspergillus.[554] Coinfection with tuberculosis and malaria have been reported.[555] [556]
• Be alert for the development of mucormycosis.[557] Diagnose and manage urgently - see the Complications section for more information.

Clinical presentation in children and adolescents

Signs and symptoms may be similar to other common viral respiratory infections and other childhood illnesses, so a high index of suspicion for COVID-19 is required in children and adolescents.

• Children and adolescents usually have fewer and milder symptoms, and they are less likely to progress to severe disease compared with adults. The reasons for this are still under investigation. Early studies suggested a higher risk of severe or critical disease in infants <1 year of age compared with children of other age groups; however, the studies had limitations and there is no conclusive evidence that younger age is a risk factor for severe disease in children and adolescents. The severity of disease caused by new variants of SARS-CoV-2, in comparison with previous lineages, remains under investigation.[27]  
• Fever, cough, and dyspnea are less common in children compared with adults.[558] Gastrointestinal symptoms are common in children. A higher prevalence of gastrointestinal symptoms has been reported in children >5 years of age compared with children ≤5 years of age.[540] The presence of diarrhea has been associated with a severe clinical course in children.[559]

Be alert for signs and symptoms of pediatric inflammatory multisystem syndrome (PIMS), also known as multisystem inflammatory syndrome in children (MIS-C).

• Consider PIMS/MIS-C in children presenting with fever and abdominal symptoms, particularly if they develop conjunctivitis or a rash. Refer to a pediatric emergency department for evaluation.[563] See the Complications section for more information.

Coinfections are possible in children.

• Coinfections were documented in 6% of children, with the most common pathogens being respiratory syncytial virus, rhinoviruses, Epstein-Barr virus, enteroviruses, influenza A, non-SARS coronaviruses, and Streptococcus pneumoniae.[564] [565]

Physical exam

Perform a physical exam.

• Patients may be febrile (with or without chills/rigors) and have obvious cough and/or difficulty breathing.

• Auscultation of the chest may reveal inspiratory crackles, rales, and/or bronchial breathing in patients with pneumonia or respiratory distress. Use caution when auscultating patients given the risk for cross-contamination. Clean the stethoscope properly between uses.[566]  

• Patients with respiratory distress may have tachycardia, tachypnea, or cyanosis accompanying hypoxia. Bradycardia has been noted in a small cohort of patients with mild to moderate disease.[567]
**Pulse oximetry**

Pulse oximetry may reveal low oxygen saturation.

- The UK National Institute for Health and Care Excellence recommends using oxygen saturation levels below 94% for adults (or below 88% for adults with known type 2 respiratory failure) and below 91% for children in room air at rest to identify people who are seriously ill.[20]
- Clinicians should be aware that patients with COVID-19 can develop "silent hypoxia": their oxygen saturations can drop to low levels and precipitate acute respiratory failure without the presence of obvious symptoms of respiratory distress.[568]

Pulse oximeters may exhibit suboptimal accuracy in certain populations.

- Limited data from studies with small numbers of participants suggest that skin pigmentation can affect pulse oximeter accuracy. In one study, occult hypoxemia (defined in the study as arterial oxygen saturation <88% by arterial blood gas despite oxygen saturation of 92% to 96% on pulse oximetry) was not detected by pulse oximetry nearly three times more frequently in Black patients compared with White patients.[544]
- The US Food and Drug Administration (FDA) has warned that multiple factors can affect the accuracy of a pulse oximeter reading (e.g., poor circulation, skin pigmentation, skin thickness, skin temperature, current tobacco use, use of fingernail polish). The FDA recommends considering accuracy limitations when using a pulse oximeter to assist in diagnosis and treatment decisions, and to use trends in readings over time rather than absolute cut-offs if possible.[569]

Traditional methods of recognizing further deterioration may not help predict those patients who go on to develop respiratory failure.

- Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognizing further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[568] While NEWS2 is still recommended for use in patients with COVID-19, the UK Royal College of Physicians now advises that any increase in oxygen requirements in these patients should trigger an escalation call to a competent clinical decision maker, and prompt an initial increase in observations to at least hourly until a clinical review happens.[570]
- A systematic review and meta-analysis found that the NEWS2 score had moderate sensitivity and specificity in predicting the deterioration of patients with COVID-19. The score showed good discrimination in predicting the combined outcome of the need for intensive respiratory support, admission to the intensive care unit, or in-hospital mortality.[571]

Pulse oximeters can be used at home to detect hypoxia.

- Home pulse oximetry requires clinical support (e.g., regular phone contact from a health professional in a virtual ward setting).
- [BMJ Practice Pointer: remote management of covid-19 using home pulse oximetry and virtual ward support] (https://www.bmj.com/content/372/bmj.n677)

**Initial laboratory investigations**

Order the following laboratory investigations in all patients with severe disease:

- ABG
Coronavirus disease 2019 (COVID-19)

Diagnosis

- CBC
- Comprehensive metabolic panel
- Thyroid function tests
- Blood glucose level
- Coagulation screen
- Inflammatory markers (e.g., serum C-reactive protein, erythrocyte sedimentation rate, interleukins, lactate dehydrogenase, procalcitonin, amyloid A, and ferritin)
- Cardiac biomarkers
- Serum creatine kinase and myoglobin.

The most common laboratory abnormalities are:[572] [573] [574]

- Lymphopenia
- Leukocytosis
- Leukopenia
- Thrombocytopenia
- Hypoalbuminemia
- Elevated cardiac biomarkers
- Elevated inflammatory markers
- Elevated D-dimer
- Abnormal liver and renal function.

Laboratory abnormalities – in particular, lymphopenia, leukocyte abnormalities, and other markers of systemic inflammation – are less common in children.[575] [576] Most patients (62%) with asymptomatic disease present with normal laboratory parameters. Of those with laboratory abnormalities, leukopenia, lymphopenia, elevated lactate dehydrogenase, and elevated C-reactive protein were the most common findings.[577]

Collect blood and sputum specimens for culture in patients with severe or critical disease.

- Cultures are required to rule out other causes of lower respiratory tract infection and sepsis, especially patients with an atypical epidemiologic history. Specimens should be collected prior to starting empiric antimicrobials if possible.[87]

Ongoing investigations

- Regularly monitor the following in hospitalized patients to facilitate early recognition of deterioration and monitor for complications:[87]
  - Vital signs (temperature, respiratory rate, heart rate, blood pressure, oxygen saturation)
  - Hematologic and biochemistry parameters
  - Coagulation parameters (D-dimer, fibrinogen, platelet count, prothrombin time)
  - ECG
  - Chest imaging
  - Signs and symptoms of venous or arterial thromboembolism.

- Patients may develop bacterial or fungal coinfections; therefore, it is important to ensure appropriate imaging is ordered and microbiologic specimens are taken when this is suspected.
SARS-CoV-2 diagnostic testing

There are three main methods for detecting SARS-CoV-2 infection:

- Molecular testing
- Serologic testing
- Rapid antigen tests.

Molecular tests are highly specific and sensitive at detecting viral RNA, and are the preferred test for confirming diagnosis in symptomatic people. However, these tests are expensive and require specialized skills and instruments, and results can take up to 24 to 48 hours. Rapid antigen tests that detect viral protein are less sensitive than molecular tests, but are faster, easier, and cheaper, and are able to detect infection in those who are most likely to be at risk of transmitting the virus. Serologic tests may be used to establish a late or retrospective diagnosis if molecular and antigen rapid tests are both negative, or may be useful surveillance tools to inform public policy. The role of these tests has evolved over the course of the pandemic. The choice of which test to use in which setting requires careful consideration of the purpose of testing and the resources available, while also balancing test characteristics of accuracy, accessibility, affordability, and the rapidity with which results are needed.\[578\]

Testing strategies vary widely between countries, and you should consult your local guidance.

**Molecular testing**

Molecular testing is required to confirm the diagnosis.

- Molecular testing is an aid to diagnosis only. The World Health Organization (WHO) recommends that healthcare providers consider a positive or negative result in combination with specimen type, clinical observations, patient history, and epidemiologic information. Where a test result does not correspond with the clinical presentation, a new specimen should be taken and retested using the same or a different molecular test (see Limitations of molecular testing below).\[579\]

Order a nucleic acid amplification test, such as real-time reverse-transcription polymerase chain reaction (RT-PCR), for SARS-CoV-2 in patients with suspected infection whenever possible.\[539\]

- Tests should be performed according to guidance issued by local health authorities and adhere to appropriate biosafety practices.
- Commonly used assays are expected to be able to detect SARS-CoV-2 variants. However, some tests may be impacted by variants.\[580\]

**Who to test**

- Base decisions about who to test on clinical and epidemiologic factors.\[539\] The World Health Organization recommends testing all people who meet the suspected case definition of COVID-19, regardless of vaccination status or disease history. When resources are constrained, people who are at risk of developing severe disease, healthcare workers, inpatients, and the first symptomatic individuals in the setting of a suspected outbreak should be prioritized. Testing of asymptomatic individuals is currently recommended only for specific groups including contacts of confirmed or probable cases and frequently exposed groups such as healthcare workers and long-term care facility workers.\[581\]
• In England, testing symptomatic people is no longer required. Guidance and eligibility for testing varies between the nations of the UK, and you should check your local guidelines. In England, testing is still recommended in the following groups:[582] [583]

- Patients in a hospital setting with symptoms or suspicion of COVID-19 to support a diagnostic pathway; for asymptomatic screening; testing on discharge to certain settings; and in patients with severe immunocompromise
- Patients on admission in unplanned care settings or preadmission in elective care settings
- Patients in the community at high risk of complications who are eligible for COVID-19 antivirals and other treatments, or where a clinician requires a test to support clinical decisions in their care
- Staff in health and social care settings for asymptomatic screening or if they develop symptoms.

• In the US, testing is recommended in:[584]

- Anyone with signs or symptoms consistent with COVID-19 (regardless of vaccination status)
- Asymptomatic people with recent known or suspected exposure to SARS-CoV-2, including those who have been in close contact (less than 6 feet [2 meters] for a total of 15 minutes or more over a 24-hour period) with a person with documented infection. Fully vaccinated people should be tested 5 to 7 days after the exposure, and people who are not fully vaccinated should be tested immediately
- Asymptomatic people without recent known or suspected exposure to SARS-CoV-2 for early identification, isolation, and disease prevention (only when screening testing is recommended by public health officials). This may include unvaccinated people who have taken part in activities that put them at higher risk because they cannot physically distance as needed to avoid exposure (e.g., travel, attending large social or mass gatherings, being in crowded or poorly ventilated indoor settings).
- Consult local health authorities for guidance as testing priorities depend on local recommendations and available resources.

Specimens

• The optimal specimen for testing depends on the clinical presentation and the time since symptom onset. The WHO recommends the following.[539]

- Upper respiratory specimens: recommended for early-stage infections, especially asymptomatic or mild cases. Nasopharyngeal swabs yield a more reliable result than oropharyngeal swabs; combined nasopharyngeal and oropharyngeal swabs further improve reliability.
- Lower respiratory specimens: recommended for later-stage infections, or patients in whom there is a strong suspicion for infection and their upper respiratory tract specimen test was negative. Suitable specimens are sputum and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease. However, consider the high risk of aerosol transmission when collecting lower respiratory specimens – an induced sputum specimen is not recommended as it may increase the risk of aerosol transmission.
- Other respiratory specimens: studies on combined oropharyngeal and nares/nasal swabs, mid-turbinate or lower nasal or nares swabs, or tongue swabs have been conducted; however, further assessment and validation is required. Oral fluid collection may be suitable
in some circumstances (e.g., young children, older patients with dementia). A systematic review and meta-analysis found that pooled nasal and throat swabs offered the best diagnostic performance of alternative sampling approaches compared with nasopharyngeal swabs for diagnosis in an ambulatory care setting. The sensitivity was 97%, the specificity was 99%, the positive predictive value was 97%, and the negative predictive value was 99%. Throat swabs gave a much lower sensitivity and positive predictive value. Self-collection was not associated with any impairment of diagnostic accuracy.[585]

- Saliva specimens: meta-analyses of paired saliva samples and nasopharyngeal swabs found no statistically significant difference in sensitivity or specificity between these specimens for SARS-CoV-2 detection, especially in the ambulatory setting. Sensitivity was not significantly different among asymptomatic people and outpatients. Methods of saliva collection may affect sensitivity. Meta-analyses demonstrate that saliva is as valid as nasopharyngeal sampling for the detection of SARS-CoV-2 infections in symptomatic and asymptomatic patients. Saliva sampling is simple, fast, noninvasive, inexpensive, and painless.[586] [587] [588] [589] [590] [591] The WHO does not currently recommend the use of saliva as the sole specimen type for routine clinical diagnostics.

- Fecal specimens: consider when upper or lower respiratory specimens are negative and the clinical suspicion for infection remains (may be used from the second week after symptom onset).

- Recommended specimen types may differ between countries. For example, in the US, the Centers for Disease Control and Prevention (CDC) recommends the following upper respiratory specimens: nasopharyngeal or oropharyngeal swab; nasal mid-turbinate swab; anterior nares swab; nasopharyngeal/nasal wash/aspirate; or saliva (self collection). Recommended lower respiratory tract specimens include: sputum, bronchoalveolar lavage, tracheal aspirate, pleural fluid, and lung biopsy.[592] [593]

- Anterior nasal swabs appear to be less sensitive (82% to 88%) compared with nasopharyngeal swabs (98%). Mid-turbinate and anterior nares swabs perform similarly.[594]

- Collect specimens under appropriate infection prevention and control procedures.

Test result

- A positive RT-PCR result confirms SARS-CoV-2 infection (in the context of the limitations associated with RT-PCR testing). If the result is negative, and there is still a clinical suspicion of infection (e.g., an epidemiologic link, typical x-ray findings, absence of another etiology), resample the patient and repeat the test. A positive result confirms infection. If the second test is negative, consider serologic testing (see below).[539]

- Genomic sequencing is not routinely recommended, but may be useful to investigate the dynamics of an outbreak, including changes in the size of an epidemic over time, its spatiotemporal spread, and testing hypotheses about transmission routes.[539] It is also useful in the context of circulating SARS-CoV-2 variants to differentiate between variants.

Complications of nasal swab testing

- Complications associated with nasal swab testing are not well characterized and data is scarce. Complications were extremely low in one study (1.24 complications per 100,000 tests). Adverse effects may include epistaxis, nasal discomfort, headache, ear discomfort, rhinorrhea, and broken
swabs being stuck (and requiring removal via nasal endoscopy). Bleeding may be life-threatening. Correct sampling techniques are crucial.[595] [596]

- Cases of iatrogenic cerebrospinal fluid leak have been reported after nasal testing in people with undiagnosed skull base defects and people with no preexisting skull base conditions.[597] [598]

Testing for other infections

- Collect nasopharyngeal swabs for testing to rule out infection with other respiratory pathogens (e.g., influenza, atypical pathogens) when clinically indicated according to local guidance. Depending on local epidemiology and clinical symptoms, test for other potential causes including malaria, dengue fever, and typhoid fever as appropriate. It is important to note that coinfections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19.[87]

**Limitations of molecular testing**

Molecular testing is an aid to diagnosis only.

- The WHO recommends that healthcare providers consider a positive or negative result in combination with specimen type, clinical observations, patient history, and epidemiologic information. It also recommends that laboratories ensure that specimens with high cycle threshold values are not incorrectly assigned a positive result due to background noise, and that they provide the cycle threshold value in the report to the healthcare provider. Disease prevalence alters the predictive value of test results. As disease prevalence decreases, the risk of a false positive increases. This means that the probability that a person who has a positive result is truly infected decreases as prevalence decreases, irrespective of the claimed specificity of the test. Careful interpretation of weak positive results is needed.[579]

Interpret RT-PCR test results with caution.

- The evidence for the use of RT-PCR in the diagnosis of COVID-19 is still emerging, and uncertainties about its efficacy and accuracy remain. Estimates of diagnostic accuracy need to be interpreted with caution in the absence of a definitive reference standard to diagnose or rule out COVID-19. Also, more evidence is needed about the efficacy of testing outside of hospital settings and in asymptomatic or mild cases.[599]

- Few studies have attempted to culture live SARS-CoV-2 virus from human samples. This is an issue because viral culture is regarded as a gold standard test against which any diagnostic index test for viruses must be measured and calibrated, to understand the predictive properties of that test.[600] Prospective routine testing of reference and viral culture specimens is necessary to establish the usefulness and reliability of RT-PCR to diagnose COVID-19, and its relation to patients factors such as date of onset of symptoms and copy threshold, in order to help predict infectivity.[601]

- As there is no clear-cut "gold standard" for COVID-19 testing, evaluating test results can be challenging. Clinical adjudication may be the best available ‘gold standard’ based on repeat swabs, history, clinical presentation, and chest imaging.[602]

It is not clear whether a positive result always indicates the presence of infectious virus.

- RT-PCR detects viral RNA, but it is not fully understood how that represents infectious virus. Complete live viruses are necessary for transmission, not the fragments identified by PCR.[601] This could ultimately lead to restrictions for people who do not present an infection risk. Because
inactivated RNA degrades slowly over time, it may still be detected many weeks after the patient is no longer infectious.[600]

- One study found that only 28.9% of positive RT-PCR SARS-CoV-2 samples demonstrated viral growth when incubated on Vero cells. There was no growth in samples with an RT-PCR cycle threshold >24, or when the symptom onset to test time was >8 days. Therefore, infectivity of patients with a cycle threshold >24 and duration of symptoms >8 days may be low.[603] Another study found that patients with a cycle threshold of 34 or above do not excrete infectious virus.[604] A systematic review found that cycle threshold values were significantly lower and log copies higher in specimens that produce live virus culture. Those with high cycle threshold are unlikely to have infectious potential.[601]

- [Centre for Evidence-Based Medicine: are you infectious if you have a positive PCR test result for COVID-19?] (https://www.cebm.net/covid-19/infectious-positive-pcr-test-result-covid-19)

Interpreting test results depends on the accuracy of the test itself, and the pre- and post-test probabilities of disease. The accuracy of the result depends on various factors including the site and quality of sampling, stage of disease, degree of viral multiplication or clearance, and disease prevalence.[602]

- Sensitivity and specificity: the pooled sensitivity has been estimated to be 87.8%, with the specificity estimated to be in the range of 87.7% to 100%.[599]
- Pretest probability: the pretest probability estimate should be made using knowledge of local rates of infection from national and regional data, as well as the patient’s symptoms, potential exposure to cases, a previous medical history of COVID-19 or the presence of antibodies, and the likelihood of an alternative diagnosis.[602] When the pretest probability is low, positive results should be interpreted with caution, and ideally a second specimen tested for confirmation.[605]
- Post-test probability: the lower the prevalence of disease in a given population, the lower the post-test probability.[606] For example, if a test with a specificity of 99% is used to test a high-risk asymptomatic population where the likelihood of infection is 50%, the positive predictive value is 99%. This means that for every 100 people with a positive test result, 99 people will have SARS-CoV-2 infection but 1 person without infection will have a false-positive result. Conversely, in a low-risk asymptomatic population where the likelihood of infection is low (e.g., 0.05%), the positive predictive value is around 4.3%. This means that for every 100 people with a positive test result, 4 to 5 people will have SARS-CoV-2 infection, but 95 to 96 people without infection will have a false-positive result.[607]

- [BMJ Practice Pointer: interpreting a covid-19 test result] (https://www.bmj.com/content/369/bmj.m1808)

False-positive results

- False-positive results can be caused by a laboratory error or a cross-reaction with antibodies formed by current and past exposure to seasonal human coronavirus infections (e.g., common cold).[608] False-positive results are more likely when the prevalence of SARS-COV-2 is moderate to low.[609]
- There are a lack of data on the rate of false-positive tests. However, preliminary estimates in the UK are in the range of 0.8% to 4%. [610] This rate could translate into a significant proportion of daily false-positive results due to the current low prevalence of the virus in the UK population, adversely affecting the positive predictive value of the test.[605]
- Examples of the potential consequences of false-positive test results include:[605]
  - Unnecessarily postponing or canceling elective procedures or treatments
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- Potential exposure to infection following a wrong pathway in hospital settings during urgent hospital admissions
- Financial losses due to self-isolation, income losses, and canceled travel
- Psychological damage due to misdiagnosis including fear of infecting others or stigmatization
- Increased depression or domestic violence due to lockdown and isolation
- Overestimating the incidence and extent of asymptomatic infection in the population.

False-negative results

- False-negative rates of between 2% and 29% have been reported.[602] A systematic review found that the false-negative rate varied across studies from 1.8% to 58% (median 11%); however, there was substantial and largely unexplained heterogeneity across studies.[611]
- The probability of a false-negative result in an infected person decreases from 100% on day 1 of infection to 67% on day 4. The median false-negative rate drops to 38% on the day of symptom onset, decreases to 20% on day 8, and then starts to increase again from day 9.[612]
- Examples of the potential consequences of false-negative test results include:[602]
  - Patients may be moved into non-COVID-19 wards leading to spread of hospital-acquired infection
  - Caregivers could spread infection to vulnerable dependents
  - Healthcare workers risk spreading the infection to multiple vulnerable individuals.

Serologic testing

Serology cannot be used as a standalone diagnostic test for acute SARS-CoV-2 infections.

- However, it may be useful in various settings (e.g., negative molecular testing, diagnosing patients with late presentation or prolonged symptoms, serosurveillance studies).[539] [613]
- [BMJ practice pointer: testing for SARS-CoV-2 antibodies] (https://www.bmj.com/content/370/bmj.m3325)

The WHO recommends collecting a paired serum sample, one specimen in the acute phase and one in the convalescent phase 2 to 4 weeks later, in patients where infection is strongly suspected and the RT-PCR result is negative.[539]

- Seroconversion or a rise in antibody titers in paired sera help to confirm whether the infection is recent and/or acute. If the initial sample tests positive, this could be due to a past infection that is not related to the current illness.
- Seroconversion may be faster and more robust in patients with severe disease compared with those with mild disease or asymptomatic infection.

The CDC recommends serologic testing as a method to support the diagnosis of illness or complications in the following situations:[614]

- A positive antibody test at least 7 days following acute illness onset in people with a previous negative antibody test (i.e., seroconversion) and who did not receive a positive viral test may indicate SARS-CoV-2 infection between the dates of the negative and positive antibody tests.
A positive antibody test can help support a diagnosis when patients present with complications of COVID-19 illness, such as multisystem inflammatory syndrome and other post-acute sequelae of COVID-19.

Assays with FDA emergency-use authorization are recommended. Serologic tests with very high sensitivity and specificity are preferred because they are more likely to exhibit high expected predictive values when administered at least 3 weeks following onset of illness.

The Infectious Diseases Society of America recommends serologic testing in the following circumstances:

- Evaluation of patients with a high clinical suspicion for infection when molecular diagnostic testing is negative and at least 2 weeks have passed since symptom onset
- Evaluation of pediatric inflammatory multisystem syndrome in children
- Serosurveillance studies.

Antibody responses to SARS-CoV-2 typically occur during the first 1 to 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.

A Cochrane review found that antibody tests for IgG/IgM only detected 30% of people with COVID-19 when the test was performed 1 week after the onset of symptoms, but accuracy increased in week 2 with 70% detected and week 3 with over 90% detected. Data beyond 3 weeks were limited. Tests gave false-positive results in 2% of patients without COVID-19. The review found that the sensitivity of antibody tests is too low in the first week since symptom onset to have a primary role in the diagnosis of COVID-19, but tests are likely to have a useful role in detecting previous infection if used 15 or more days after symptom onset (although there were very little data beyond 35 days).

**Limitations of serologic testing**

The evidence for the use of antibody tests in the diagnosis of COVID-19 is still emerging, and uncertainties about their efficacy and accuracy remain.

- Estimates of diagnostic accuracy need to be interpreted with caution in the absence of a definitive reference standard to diagnose or rule out COVID-19. More evidence is needed about the efficacy of testing outside of hospital settings and in asymptomatic or mild cases. The estimated sensitivity of antibody tests ranged from 18.4% to 96.1% (the lowest reported sensitivity was from a point-of-care test, although a sensitivity <50% was reported for one laboratory test), and specificity ranged from 88.9% to 100%.

Understanding of the antibody response to SARS-CoV-2 is still emerging; therefore, antibody detection tests must be used with caution, and not used to determine acute infections.

- Results do not indicate the presence or absence of current or previous infection with certainty as IgM and IgG antibodies may take 1 to 3 weeks to develop after infection. A reliable diagnosis is often only possible in the recovery phase when opportunities for management or interruption of transmission have passed.

- The duration of the persistence of antibodies produced in response to SARS-CoV-2 is still under investigation. The presence of antibodies that bind to SARS-CoV-2 does not guarantee that they are neutralizing antibodies, or that they offer protective immunity.

- Although an antibody test may employ a specific antigen(s), antibodies developed in response to different proteins may cross-react (i.e., the antigen may detect antibodies it is not intended to
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Therefore, it may not provide sufficient information on the presence of antigen-specific antibodies.[614]

- Vaccination may cause false-positive results for tests that utilize the S antigen or subunits like receptor-binding domains, but not for tests that use the N antigen.[614]

Rapid diagnostic tests

Antigen detection

- Antigen testing relies on direct detection of SARS-CoV-2 viral proteins in upper respiratory specimens or saliva using a lateral flow immunoassay.[619]
  
  - Results are usually available in less than 30 minutes.
  - While antigen tests are substantially less sensitive than RT-PCR, particularly in asymptomatic people, they offer the possibility of rapid, inexpensive, and early detection of the most infectious cases in appropriate settings.
  - Antigen testing is recommended in settings likely to have the most impact on early detection of cases for care and contact tracing, and where test results are most likely to be correct.
  - International guidelines on the use of rapid antigen tests vary. Consult your local guidance.
  
  - The WHO recommends antigen testing for primary case detection, for contact tracing, during outbreak investigations, and to monitor trends of disease incidence in communities. Tests should meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared with an RT-PCR reference assay. Antigen testing should be prioritized for use in symptomatic people who meet the case definition in the first 5 to 7 days of symptom onset, and to test asymptomatic people at high risk of infection, including contacts and health workers, particularly in settings where molecular testing capacity is limited. Results are most reliable in areas where there is ongoing community transmission.[619] Self-testing should be offered in addition to professionally administered testing services. It should always be voluntary and never mandatory or coercive.[620]
  
  - In the UK, rapid antigen tests are recommended in certain situations, including: before visiting people who are at higher risk of severe disease; for contacts of a confirmed case who do not have to self-isolate; and for people who will be in high-risk situations on a particular day (e.g., in crowded and enclosed spaces, or if there is limited fresh air).[621]
  
  - In the US, the Infectious Diseases Society of America recommends antigen testing in some individuals only when molecular testing is not readily available or is logistically infeasible, noting that the overall quality of available evidence supporting its use was graded as very low to moderate.[622] The CDC recommends that antigen tests may be used in congregate and community settings; however, confirmatory molecular testing may be needed.[623] The FDA has warned that false-positive results can occur with antigen tests, including when users do not follow the instructions for use, and that the number of false-positive tests increases as disease prevalence decreases.[624]
  
  - Evidence for the use of rapid antigen tests is emerging.

  - A Cochrane review found that rapid antigen tests vary in sensitivity. Sensitivity was higher in the first week after symptom onset in symptomatic people (78.3%), compared with the second week of symptoms (51%). Sensitivity was higher in those with RT-PCR cycle
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Threshold values ≤25 (94.5%), compared with those with cycle threshold values >25 (40.7%). Sensitivity was higher in symptomatic people (72%), compared with asymptomatic people (58.1%). Sensitivity also varied between brands of tests. Positive predictive values suggest that confirmatory testing of those with positive results may be considered in low prevalence settings. Evidence for testing in asymptomatic cohorts was limited, and no studies assessed the accuracy of repeated lateral flow testing or self-testing.[625]

- A systematic review found that the performance of lateral flow tests is heterogenous and depends on the manufacturer. Sensitivity ranged between 37.7% to 99.2%, with specificity ranging between 92.4% to 100% across studies.[626]
- A systematic review and meta-analysis found that the pooled overall diagnostic sensitivity and specificity of rapid antigen tests in pediatric populations was 64.2% and 99.1%, respectively. Sensitivity was higher in symptomatic children compared with asymptomatic children.[627]
- An observational cohort study that assessed the performance of rapid antigen lateral flow testing against RT-PCR in an asymptomatic general population in the UK found that the lateral flow test can be useful for detecting infections among asymptomatic adults, particularly those with a high viral load who are likely to be infectious. Lateral flow tests showed a sensitivity of 40%, specificity of 99.9%, positive predictive value of 90.3%, and negative predictive value of 99.2% in this population. Approximately 10% of people with a higher viral load detected by RT-PCR were missed by lateral flow tests.[628]
- Rapid antigen testing appears to be a reliable diagnostic tool to quickly detect people with a high viral load and in the first week of symptom onset, and can help to detect and isolate potential superspreaders before RT-PCR results are available. However, testing is unsuccessful in detecting people with lower viral load and asymptomatic patients.[629] [630]

- Laboratory-based (nonrapid) antigen tests are also available in some countries.

**Molecular testing**

- Rapid molecular tests are available. Some rapid molecular tests show accuracy levels similar to laboratory-based RT-PCR tests with high sensitivity and specificity. However, there is limited evidence available to support their use in symptomatic people, and there is no evidence for their use in asymptomatic populations. Resource implications of their use at scale are potentially high. Rapid molecular tests may be suitable for some testing scenarios (e.g., where obtaining test results within 2 hours will enable appropriate decision-making).[625]

**Antibody detection**

- While rapid antibody detection kits have been approved for the qualitative detection of SARS-CoV-2 IgG/IgM antibodies in serum, plasma, or whole blood, the WHO does not recommend the use of these tests outside of research settings as they have not been validated as yet.[631]
- Evidence is particularly weak for point-of-care serologic tests. A meta-analysis found that the overall sensitivity of chemiluminescent immunoassays (CLIA) for IgG or IgM was approximately 98%, and the sensitivity of enzyme-linked immunosorbent assays (ELISA) was 84%; however, lateral flow immunoassays (LIFA), which have been developed as point-of-care tests, had the lowest sensitivity at 66%. Test sensitivity was highest 3 or more weeks after onset of symptoms. Available evidence does not support the use of existing point-of-care serologic tests.[632]
Chest imaging

All imaging procedures should be performed according to local infection prevention and control procedures to prevent transmission. Chest imaging is considered safe in pregnant women.[633]

Order a chest x-ray in all patients with suspected pneumonia.

- Approximately 74% of patients have an abnormal chest x-ray at the time of diagnosis. The most common abnormalities are ground-glass opacity (29%) and consolidation (28%). Distribution is generally bilateral, peripheral, and basal zone predominant. Pneumothorax and pleural effusions are rare. There is no single feature on chest x-ray that is diagnostic.[634]
- Chest x-ray is moderately sensitive and moderately specific for the diagnosis of COVID-19. Pooled results found that chest x-ray correctly diagnosed COVID-19 in 80.6% of people who had the disease. However, it incorrectly identified COVID-19 in 28.5% of people who did not have the disease.[635]
- Although chest x-ray appears to have a lower sensitivity compared with chest CT, it has the advantages of being less resource-intensive, associated with lower radiation doses, easier to repeat sequentially, and portable.[636]

Consider ordering a CT scan of the chest.

- Chest CT may play a role in diagnosis in a limited number of hospitalized patients, particularly when initial molecular testing has been inconclusive, or when an alternative diagnosis is being considered.[637] However, it is not diagnostic for COVID-19 and local guidance should be consulted on whether to perform a CT scan.

  - The British Society of Thoracic Imaging (BSTI) recommends CT imaging in patients with clinically suspected COVID-19 who are seriously ill if chest x-ray is uncertain or normal. Without the suspicion of COVID-19, the radiology is nonspecific and could represent many other disease processes. The BSTI in collaboration with NHS England have produced a radiology decision support tool to help clinicians decide whether or not chest imaging should be ordered.[542] [BSTI: radiology decision tool for suspected COVID-19] (https://www.bsti.org.uk/media/resources/files/NHSE_BSTI_APPROVED_Radiology_on_CoVid19_v6_modified1__-_Read-Only.pdf)

  - Some institutions in the UK recommend a more pragmatic approach for patients with high clinical suspicion of COVID-19, with chest CT recommended only after two indeterminate or normal chest x-rays in combination with a negative RT-PCR test.[638]

  - The American College of Radiology recommends reserving CT for hospitalized, symptomatic patients with specific clinical indications for CT, and emphasizes that a normal chest CT does not mean that a patient does not have COVID-19 and that an abnormal chest CT is not specific for COVID-19 diagnosis.[639]

  - Chest CT is sensitive and moderately specific for the diagnosis of COVID-19. Pooled results found that chest CT correctly diagnosed COVID-19 in 87.9% of people who had the disease. However, it incorrectly identified COVID-19 in 20% of people who did not have the disease. Therefore, chest CT may have more utility for excluding COVID-19 than for differentiating it from other causes of respiratory illness.[635] Accuracy appears to be lower among children; however, there are limited data in this population.[637]

  - Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[640] Some patients may present with a normal chest finding despite a positive RT-
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- PCR. Results of RT-PCR testing may be false-negative, so patients with typical CT findings should have repeat RT-PCR testing to confirm the diagnosis.

- CT imaging abnormalities may be present in asymptomatic patients. The pooled estimate of the rate of positive chest CT findings in asymptomatic cases was 47.6% (mainly ground-glass opacity).

- Pregnant women appear to present more commonly with more advanced CT findings compared with the general adult population; however, results are similar to those in the general adult population.

**Typical features of chest CT**

- Abnormal chest CT findings have been reported in up to 97% of COVID-19 patients in one meta-analysis of 50,466 hospitalized patients.

- The most common findings are ground-glass opacity, either in isolation or coexisting with other findings such as consolidation, interlobular septal thickening, or crazy-paving pattern. The most common distribution pattern is bilateral, peripheral/subpleural, posterior distribution of the opacities, with a lower lobe predominance. Extensive/multilobar involvement with consolidations is more common in older patients and those with severe disease.

- Ground-glass opacity has the highest diagnostic performance for COVID-19 pneumonia, followed by ground-glass opacity plus consolidation, and consolidation only. The simultaneous presence of ground-glass opacity and other features of viral pneumonia had optimum performance in the detection of COVID-19 (sensitivity 90% and specificity 89%).

- CT scan generally shows an increase in the size, number, and density of ground-glass opacities in the early follow-up period, with a progression to mixed areas of ground-glass opacities, consolidations, and crazy paving peaking at day 10 to 11, before gradually resolving or persisting as patchy fibrosis.

- A small comparative study found that patients with COVID-19 are more likely to have bilateral involvement with multiple mottling and ground-glass opacity compared with other types of pneumonia.

- Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity, nonspecific patchy shadows, areas of consolidation, infected nodules, and a halo sign. Abnormalities are more common in multiple lobes and are predominantly bilateral. Pleural effusion is rare. Children may have signs of pneumonia on chest imaging despite having minimal or no symptoms. Ground-glass opacity and peribronchial thickening were the most prevalent findings in infants younger than 1 year of age.

**Atypical features of chest CT**

- Pulmonary vascular enlargement, interlobular or intralobular septal thickening, adjacent pleural thickening, air bronchograms, subpleural lines, crazy-paving pattern, bronchus distortion, bronchiectasis, vacuolar retraction sign, and halo sign are atypical features. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have also been reported rarely.

The WHO recommends chest imaging in the following scenarios:

- Symptomatic patients with suspected COVID-19 when RT-PCR is not available, RT-PCR test results are delayed, or initial RT-PCR testing is negative but there is a high clinical suspicion for COVID-19 (for diagnosis)
• Patients with suspected or confirmed COVID-19 who are not currently hospitalized and have mild symptoms (to decide on hospital admission versus home discharge)
• Patients with suspected or confirmed COVID-19 who are not currently hospitalized and have moderate to severe symptoms (to help decide on regular ward admission versus intensive care unit admission)
• Patients with suspected or confirmed COVID-19 who are currently hospitalized and have moderate to severe symptoms (to inform therapeutic management).

Emerging investigations

Lung ultrasound

• Lung ultrasound is used as a diagnostic tool in some centers as an alternative to chest x-ray and chest CT. Although there is only very low-certainty evidence supporting its diagnostic accuracy, it might be helpful as a supplemental or alternate imaging modality.[636]
• Ultrasound is sensitive but not specific for the diagnosis of COVID-19. Pooled results found that lung ultrasound correctly diagnosed COVID-19 in 86.4% of people with the disease. However, it incorrectly diagnosed COVID-19 in 45% of people who did not have the disease. Therefore, ultrasound may have more utility for excluding COVID-19 than for differentiating it from other causes of respiratory illness.[635]
• B-lines (confluent or separated and usually at least 3) and pleural abnormalities, with a bilateral distribution, are the most frequent findings in COVID-19. Other findings include consolidations, pleural effusion, air bronchogram, and pneumothorax.[652] While these findings are not specific for COVID-19, they may increase the likelihood of disease in the context of a characteristic clinical presentation.
• It has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, easier sterilization process, absence of ionizing radiation exposure, and repeatability during follow-up. It may also be more readily available in resource-limited settings. However, it also has some limitations (e.g., it is unable to discern chronicity of a lesion) and other imaging modalities may be required. Ultrasound may be used in pregnant women and children.[653] [654] [655]
• Possible roles for ultrasound include: reducing nosocomial transmission; monitoring progress of patients; and a possible role in subpopulations who are vulnerable but are not suitable for CT (e.g., pregnant women).[656] Lung ultrasound score may play a role in prognosis.[657]

Reverse transcription loop-mediated isothermal amplification

• Reverse transcription loop-mediated isothermal amplification (RT-LAMP) assays are an emerging test to detect SARS-CoV-2 viral RNA. While assays are simple and quick, there is less evidence for their use. Assays for SARS-CoV-2 have been developed and are being evaluated.[658] [659] [660]
• RT-LAMP appears to be a reliable assay, comparable to RT-PCR, particularly with medium to high viral loads (i.e., cycle threshold <35), especially in resource-limited settings.[661] A sensitivity of 95.5% and specificity of 99.5% has been reported.[662]

CRISPR-based diagnostics

• Clustered regularly interspaced short palindromic repeats (CRISPR)-based diagnostic methods have been developed for detecting SARS-CoV-2 viral RNA. These simple, high-throughput
molecular tests have the advantage of providing results in less than 1 hour, can be used with various specimens, and have high specificity/sensitivity (similar to RT-PCR).[663][664][665]  
- Various CRISPR-based tests have been granted emergency-use authorization by the US Food and Drug Administration.

**Breathalyzers**

- Breath analysis has been shown to have potential in diagnosing COVID-19 by analyzing volatile organic compounds in exhaled breath.[666]  
- The US Food and Drug Administration has issued an emergency-use authorization for the first COVID-19 diagnostic test that detects chemical compounds in breath samples associated with SARS-CoV-2 infection. The test has been shown to have 91.2% sensitivity and 99.3% specificity in one company-sponsored study of 2409 participants, including those with and without symptoms.[667] However, the test currently has many limitations (e.g., size of the device, number of samples that can be processed, lack of evidence for this method of diagnosis, other diseases or food/drinks that can affect result, test result is presumptive and still requires confirmation), and more research is required.

**Viral isolation**

- Viral isolation is not recommended as a routine diagnostic procedure. All procedures involving viral isolation in cell culture require trained staff and biosafety level 3 (BSL-3) facilities.[539]

**Calprotectin**

- Calprotectin is an emerging biomarker of interest. Calprotectin levels often increase following infection or trauma, and in inflammatory disease. Serum/fecal calprotectin levels have been demonstrated to be significantly elevated in COVID-19 patients with severe disease, and it may have prognostic significance.[668][669]

**History and exam**

**Key diagnostic factors**

**fever (common)**

- Reported in approximately 77% of patients.[670] In one case series, only 44% of patients had a fever on presentation, but it developed in 89% of patients after hospitalization.[671] The course may be prolonged and intermittent, and some patients may have chills/rigors. The prevalence of fever is higher in adults compared with children; approximately 54% of children do not exhibit fever as an initial presenting symptom.[672] In children, fever may be absent or brief and rapidly resolving.[673]

**cough (common)**

- Reported in approximately 68% of patients.[670] The cough is usually dry; however, a productive cough has been reported in some patients. Can persist for weeks or months after infection.[674]

**dyspnea (common)**

- Reported in approximately 38% of patients.[670] Median time from onset of symptoms to development of dyspnea is 5 to 8 days.[47][48][675] May last weeks after initial onset of symptoms. Wheeze has been reported in 17% of patients.[676]
altered sense of smell/taste (common)

- Presence of anosmia and/or ageusia may be useful as a red flag for diagnosis, particularly in countries with older circulating SARS-CoV-2 variants.[538] However, loss of smell, a pathognomonic feature of previous SARS-CoV-2 variants, was present in only <20% of cases of people infected with the Omicron variant.[547]
- Anosmia or hyposmia has been significantly associated with an enhanced risk of testing positive for COVID-19, and may be a good predictor of infection.[677] Olfactory dysfunction (anosmia/hyposmia) has been reported in approximately 55% of patients, and gustatory dysfunction (ageusia/dysgeusia) has been reported in approximately 41% of patients in the context of previously circulating SARS-CoV-2 variants.[678] Prevalence appears to be higher in European studies.[679] May be an early symptom before the onset of other symptoms, or may be the only symptom in patients with mild to moderate illness.[680] Prevalence of anosmia/ageusia presenting before other symptoms was 13% to 73%, at the same time as other symptoms was 14% to 39%, and after other symptoms was 27% to 49%.[681]
- Olfactory recovery was found to occur as early as 7 days, with the majority of patients recovering within 30 days.[682] Persistent anosmia has an excellent prognosis with nearly complete recovery at 1 year.[683] In one cohort study, 12.8% of previously hospitalized patients in the UK reported persistent problems with smell or taste up to 1 year after infection.[684] Parosmia (misperception of an odor) is a late-onset symptom that may develop approximately 3 months after infection. It may occur without any preceding apparent smell loss, or it may follow a short recovery period from initial anosmia.[685]
- Many drugs are associated with taste and smell changes (e.g., antibiotics, ACE inhibitors) and should be considered in the differential diagnosis.[686]
- Smell and taste dysfunction are common in children.[687]

Other diagnostic factors

headache (common)

- Reported in approximately 25% of patients. Headache is twice as prevalent in COVID-19 patients compared with patients with non-COVID-19 viral respiratory tract infections.[688]
- Data from the UK COVID Symptom Study report that headache is one of the most common symptoms in fully vaccinated people and unvaccinated people in the context of the Delta and Omicron variants.[545] [546]

sore throat (common)

- Reported in approximately 16% of patients.[670] Usually presents early in the clinical course.
- Data from the UK COVID Symptom Study report that sore throat is one of the most common symptoms in fully vaccinated people and unvaccinated people in the context of the Delta and Omicron variants.[545] [546]

rhinorrhea/nasal congestion (common)

- Rhinorrhea has been reported in approximately 8% of patients, and nasal congestion has been reported in approximately 5% of patients.[676]
- Data from the UK COVID Symptom Study report that rhinorrhea is one of the most common symptoms in fully vaccinated people and unvaccinated people in the context of the Delta and Omicron variants.[545] [546]

sneezing (common)
• Data from the UK COVID Symptom Study report that sneezing is one of the most common symptoms in fully vaccinated people in the context of the Delta and Omicron variants.[545] [546]

fatigue (common)
• Reported in approximately 30% of patients.[670] Patients may also report malaise. Fatigue and exhaustion may be extreme and protracted, even in patients with mild disease.
• Data from the UK COVID Symptom Study report that mild to severe fatigue is one of the most common symptoms in the context of the Omicron variant.[546]

myalgia or arthralgia (common)
• Reported in approximately 17% (myalgia) and 11% (arthralgia) of patients.[676] Arthritis has been reported rarely.[689] [690]

sputum production/expectoration (common)
• Reported in approximately 18% of patients.[670]

chest tightness (common)
• Reported in approximately 22.9% of patients.[573]

gastrointestinal symptoms (common)
• Reported in 20% of patients. The weighted pooled prevalence of specific symptoms is as follows: loss of appetite 22.3%; diarrhea 2.4%; nausea/vomiting 9%; and abdominal pain 6.2%. Gastrointestinal symptoms appear to be more prevalent outside of China, although this may be due to increased awareness and reporting of these symptoms as the pandemic progressed.[691] Gastrointestinal symptoms are not associated with an increased likelihood for testing positive for COVID-19; however, anorexia and diarrhea, when combined with loss of smell/taste and fever, were 99% specific for COVID-19 infection in one prospective case-control study.[692] The presence of gastrointestinal symptoms may be a predictor of progression to severe disease.[693] [694] However, the presence of these symptoms does not appear to affect intensive care unit admission rate or mortality.[695] [696] The presence of diarrhea has been associated with a severe clinical course in children.[559] Hematochezia has been reported.[697]

dizziness (common)
• Reported in approximately 11% of patients.[676]

neurologic symptoms (common)
• Confusion has been reported in approximately 11% of patients.[676] The overall prevalence of delirium is 24.3%, with an increased prevalence in adults >65 years of age (28%). Delirium has been associated with a 3-fold increase in mortality.[698] Benzodiazepine use and the lack of family visitation (virtual or in-person) have been identified as risk factors for delirium.[699] The pooled prevalence of anxiety, depression, and insomnia is 15.2%, 16%, and 23.9%, respectively.[700] Altered mental status was as common in younger hospitalized patients (<60 years) as it was in older patients in one study.[701]

ocular symptoms (common)
• Reported in 11% of patients. The most common ocular symptoms include dry eye or foreign body sensation (16%), redness (13.3%), tearing (12.8%), itching (12.6%), eye pain (9.6%), and discharge
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(8.8%). Conjunctivitis was the most common ocular disease in patients with ocular manifestations (88.8%).[702] Most symptoms are mild and last for 4 to 14 days with no complications. Prodromal symptoms occur in 12.5% of patients.[703] Mild ocular symptoms (e.g., conjunctival discharge, eye rubbing, conjunctival congestion) were reported in 22.7% of children in one cross-sectional study. Children with systemic symptoms were more likely to develop ocular symptoms.[704] Patients with severe disease are more likely to have ocular symptoms.[705] Retinal complications that may lead to vision loss have also been reported.[706] [707] [708]

audio-vestibular symptoms (uncommon)

- Sudden sensorineural hearing loss, tinnitus, and rotatory vertigo have been reported in 7.6%, 14.8%, and 7.2% of patients, respectively. Otalgia has also been reported.[709]

chest pain (uncommon)

- Reported in approximately 7% of patients.[676] May indicate pneumonia.

hemoptysis (uncommon)

- Reported in approximately 2% of patients.[676] May be a symptom of pulmonary embolism.[710]

bronchial breath sounds (uncommon)

- May indicate pneumonia.

tachypnea (uncommon)

- May be present in patients with acute respiratory distress.

tachycardia (uncommon)

- May be present in patients with acute respiratory distress.

cyanosis (uncommon)

- May be present in patients with acute respiratory distress.

crackles/rales on auscultation (uncommon)

- May be present in patients with acute respiratory distress.

cutaneous symptoms (uncommon)

- The pooled prevalence of overall cutaneous lesions is 5.7%. The most common symptoms are a viral exanthem-like presentation (4.2%), maculopapular rash (3.8%), and vesiculobullous lesions (1.7%). Other manifestations include urticaria, chilblain-like lesions, livedo reticularis, and finger/toe gangrene.[711] [712] In the UK COVID Symptom Study, 17% of respondents reported rash as the first symptom of disease, and 21% of respondents reported rash as the only clinical sign.[713] Cutaneous signs may be the only, or the first, presenting sign.[714] Cutaneous symptoms have been reported in children.[715] It is unclear whether skin lesions are from viral infection, systemic consequences of the infection, or drugs the patient may be on. Further data is required to better understand cutaneous involvement and whether there is a causal relationship. No direct link between COVID-19 and chilblains has been established, and there is conflicting evidence.[716] [717] [718]


oral mucosal lesions (uncommon)
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- Aphthous, hemorrhagic, and necrotic ulcers have been reported in 36.3% of patients. Other lesions include pustules, macules, bullae, maculopapular enanthema, and erythema multiforme-like lesions.[719] SARS-CoV-2–associated reactive infectious mucocutaneous eruption has also been reported.[720] Severe and potential life-threatening mucocutaneous dermatologic manifestations have also been reported.[721] It is unclear whether oral lesions are from viral infection, systemic consequences of the infection, secondary to existing comorbidities, or drugs the patient may be on.[722]

lower urinary tract symptoms (uncommon)

- There is emerging evidence that patients may rarely have signs, symptoms, and radiologic and laboratory features indicative of involvement of the lower urinary tract and male genital system. This may include scrotal discomfort, swelling, or pain (acute orchitis, epididymitis, or epididymo-orchitis), low-flow priapism, impaired spermatogenesis, bladder hemorrhage, acute urinary retention, and worsening of existing lower urinary tract symptoms (including exacerbation of benign prostatic hyperplasia). Further research is required.[723] [724]

Risk factors

Strong

contact with probable or confirmed case

- People who have been in contact with a probable or confirmed case are at increased risk of infection.
- The World Health Organization defines a contact as a person who has experienced any one of the following exposures: face-to-face contact with a probable or confirmed case within 3 feet (1 meter) and for at least 15 minutes; direct physical contact with a probable or confirmed case; direct care for a patient with probable or confirmed COVID-19 without using recommended personal protective equipment; or other situations as indicated by local risk assessments. Exposure must have occurred during the infectious period of the case. For symptomatic cases, this means 2 days before and 10 days after symptom onset of the case, plus at least 3 additional days without symptoms, for a minimum of 13 days total after symptom onset. For asymptomatic cases, this means 2 days before and 10 days after the date on which the sample that led to confirmation was taken.[124]
- The Centers for Disease Control and Prevention defines a close contact as someone who has been within 6 feet (2 meters) of an infected person for at least 15 minutes over a 24-hour period, beginning 2 days before symptom onset (or 2 days before testing in asymptomatic patients).[125]

residence/work/travel in location with high risk of transmission

- People who live or work in, or travel to, a location with a high risk of transmission are at increased risk of infection.
- People residing or working in an area with a high risk of transmission (e.g., closed residential settings, humanitarian setting), people residing in or traveling to an area with community transmission, and people working in a health setting (including within health facilities and households) at any time within the 14 days prior to symptom onset are at higher risk of infection.[124]

older age

- Older people are at increased risk for infection and severe disease.[126]
- The risk of hospitalization and death increases with age. An increased age-related risk of in-hospital mortality, case mortality, and hospitalization of 5.7%, 7.4%, and 3.4% per age year, respectively, has
been observed, based on high-quality of evidence. No increased risk was observed for intensive care unit admission and intubation by age year. There was no evidence of a specific age threshold at which the risk accelerates considerably.[127]

- According to US data, the risk of hospitalization is 10 times higher and the risk of death is 340 times higher in people ages 85 years and older compared with 18- to 29-year-olds.[128]
- In the UK, data from a cross-sectional study indicated that people ages 40 to 64 years are at greatest risk of infection, followed by patients 75 years and older, and then people ages 65 to 74 years.[129] The highest mortality rate was observed in patients 80 years and older.[130]
- In the US, patients ≥65 years accounted for 31% of all cases, 45% of hospitalizations, 53% of intensive care unit admissions, and 80% of deaths early in the pandemic, with the highest incidence of severe outcomes in patients ages ≥85 years.[25]
- While age is an independent risk factor, the risk in older people is also partly related to the likelihood that older adults are more likely to have comorbidities. The higher prevalence of malnutrition in older patients may also contribute to poor outcomes.[131]

**male sex**

- Males are at increased risk for infection and severe disease.[126]
- A meta-analysis found that men have a higher risk for infection, hospitalization, disease severity, intensive care unit admission, and death.[132]
- It has been hypothesized that this may be due to the presence of androgens, a lower level of SARS-CoV-2 antibodies compared with females, women mounting a stronger immune response compared with men, genetic factors, a higher prevalence of alcohol consumption and smoking, or higher circulating levels of inflammatory cytokines; however, further research is required.[133][134][135]

**ethnicity**

- People who belong to racial/ethnic minority populations are at increased risk of infection, severe disease, hospitalization, and death.[136][137][138] However, studies are inconsistent, particularly in regards to the definitions of racial/ethnic minority groups and socioeconomic status.
- In the UK, data indicate that South Asian, Black, and mixed ethnicity populations have an increased risk for testing positive and of adverse outcomes (i.e., hospitalization, intensive care unit admission, death) compared with the White population, even after accounting for differences in sociodemographic, clinical, and household characteristics.[139] Race may play an important role in adverse outcomes in children as well as adults.[140]
- In the US, American Indian or Alaskan Native, Latino, Black, and Asian or Pacific Islander people were more likely than White people to test positive, be hospitalized, be admitted to the intensive care unit, or die during the first year of the pandemic.[141][142]
- Risk factors in these patients include poverty, low level of education, poor housing conditions, low family income, speaking in a language other than the national language, and household overcrowding.[138]
- While the risk of diagnosis was higher in most ethnic minorities, once hospitalized, no clear inequalities in outcomes existed (except for the high risk of mortality in ethnic minorities in Brazil). This suggests that ethnic minority status is an important social determinant of COVID-related health outcomes, likely through association with other social determinants (e.g., housing, socioeconomic status, employment, general health status).[143] Racial disparities in outcomes may also be partially attributed to higher rates of comorbidities in certain ethnic groups.[144]
residence in a long-term care facility

- People in a long-term care facility are at increased risk for infection and severe disease.[145] [146]
- In the UK, care home residents represented approximately one third of the total number of deaths in England and Wales during the first wave of the pandemic; other countries reported a similar experience. This was likely due to shortages in personal protective equipment, a vulnerable population, and a lack of testing.[147] A study across four nursing homes found that 26% of residents died over a 2-month period, with all-cause mortality increasing by 203% compared with previous years. Approximately 40% of residents tested positive for SARS-CoV-2, and of these, 43% were asymptomatic and 18% had atypical symptoms.[148]
- In the US, the 30-day all-cause mortality rate was 21% in a cohort study of more than 5000 nursing home residents. Older age, male sex, and impaired cognitive and physical function were independently associated with mortality.[149]

presence of comorbidities

- People with comorbidities are at increased risk for severe disease, and the more comorbidities, the greater the risk.[150] [146]
- In the UK, the most common comorbidities reported in a cohort study of more than 20,000 hospitalized patients were cardiac disease (31%), uncomplicated diabetes (21%), nonasthmatic chronic pulmonary disease (18%), and chronic kidney disease (16%).[24] Among 65,000 patients hospitalized in the UK, 68% reported at least one cardiometabolic condition on admission. Baseline cardiometabolic conditions were associated with an increased risk of in-hospital complications, and this risk increased in the presence of cardiometabolic multimorbidity.[151]
- In the US, approximately 95% of hospitalized adults had at least one reported underlying medical condition, with the most common being hypertension, disorders of lipid metabolism, and obesity. Approximately 99% of patients who died had at least one underlying health condition. The strongest risk factors for death were obesity, anxiety and fear-related disorders, and diabetes, as well as the total number of underlying conditions.[152] It has been estimated that approximately 56% of adults, and 32% of young adults (ages 18-25 years), are at risk for severe disease because of the presence of at least one comorbidity.[153] [154]
- Globally, hypertension (21%), obesity (18%), and diabetes (18%) were the most prevalent comorbidities. Cancer, chronic kidney disease, diabetes, and hypertension were independently associated with mortality. Chronic kidney disease was statistically the most prominent comorbidity leading to death.[155] Metabolic syndrome is also significantly associated with a higher risk of mortality.[156]
- Children with comorbidities including obesity, diabetes, chronic lung disease (not including asthma), heart disease, seizure disorders, and immunocompromised status had a high prevalence of severe disease.[157]

obesity

- People with obesity (≥30 kg/m²) and people who are overweight (25-30 kg/m²) are at increased risk of infection and severe disease.[146] [158]
- Of the 2.5 million deaths reported globally by the end of February 2021, 2.2 million were in countries where more than half the population is classified as overweight. In countries where less than half the adult population is classified as overweight, the likelihood of death is around one tenth of the level seen in countries where more than half the population is classified as overweight.[159]
Coronavirus disease 2019 (COVID-19)

Diagnosis

- Evidence from a meta-analysis found that patients who are obese have a significantly increased risk of infection, clinically severe disease, hospitalization, intensive care unit admission, need for mechanical ventilation, and mortality.[158]
- A cohort study in the UK found that the risk of severe outcomes (i.e., hospitalization, intensive care unit admission, death) increased progressively above a body mass index ≥23 kg/m², independent of the excess risks of related diseases (e.g., diabetes). The relative risk was particularly notable in people <40 years of age and those with Black ethnicity. Every unit increase in body mass index increased the risk of: hospital admission by 5% (above body mass index ≥23 kg/m²); intensive care admission by 10% (any body mass index); and death by 4% (body mass index ≥28 kg/m²).[160]
- A cohort study in the US found a nonlinear relationship between body mass index and disease severity, with the lowest risk at body mass indexes near the threshold between healthy weight and overweight, then increasing with higher body mass index.[161]

Cardiovascular disease

- People with cardiovascular disease are at increased risk for severe disease.[146]
- Preexisting cardiovascular disease is associated with adverse outcomes including disease severity, disease progression, and mortality.[162]
- Arrhythmias, coronary artery disease, and cardiovascular disease are significantly associated with intensive care unit admission. Heart failure, arrhythmias, coronary artery disease, and cardiovascular disease are also significantly associated with an increased risk of mortality.[163] Preexisting atrial fibrillation/atrial flutter was associated with a higher risk of intensive care admission, in-hospital mortality, and worse outcomes.[164] [165] Coronary heart disease has also been associated with disease progression and severe/critical disease. The association is affected by the presence of hypertension; patients with coronary heart disease and hypertension had an increased risk of poor prognosis compared with those without hypertension.[166]
- People with risk factors for cardiovascular disease (e.g., hypertension, diabetes) are also at increased risk for severe disease and mortality (see below).[167] [168]

Diabetes

- People with type 1 or type 2 diabetes are at increased risk for severe disease.[146]
- Diabetes is associated with a more than 2-fold increase in the risk for severe disease, and a slightly less than 2-fold increase in the risk for death. Diabetes is also associated with an increased risk for intensive care unit admission. Individual studies show that type 1 diabetes is associated with a higher risk of death compared with type 2 diabetes. Higher blood glucose levels (in the immediate and longer terms) are associated with worse outcomes. There is no evidence of difference in risk between people with new-onset and preexisting diabetes. Data are insufficient to determine whether diabetes predisposes people to infection. There are no data to suggest that diabetes increases the risk of severe disease in children and adolescents.[169] Variability across different regions in the world is significant and may skew overall trends.[170]
- Risk factors for poor prognosis and higher mortality in patients with diabetes are similar to risk factors that exist in the general population and include older age, male sex, non-White ethnicity, socioeconomic deprivation, acute kidney injury, history of stroke or heart failure, and higher body mass index. Other more specific risk factors include prediabetes, poor glycemic control, higher glycosylated hemoglobin level, diabetic ketoacidosis, hyperglycemic hyperosmolar state, diabetic retinopathy, and insulin use.[171] [172] [173] [174] [175] [176] [177] Studies that adjusted for age, sex, ethnicity, deprivation, and geographic location still found an increased risk for death in people with diabetes. There is little evidence regarding the role of comorbidities in increasing the risk of poor outcomes.[169]
• Use of metformin, sodium–glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists was associated with lower mortality in patients with type 2 diabetes. Dipeptidyl peptidase-4 inhibitors and insulin have been associated with increased mortality. Sulfonylureas, thiazolidinediones, and alpha-glucosidase inhibitors did not appear to increase or decrease risk of mortality.\[178\] It is unclear whether these drugs have a protective effect, and further investigation is required.

• Poor outcomes in these patients may be due to the syndromic nature of diabetes, the presence of comorbidities, impaired immune function, possible upregulation of enzymes that mediate viral invasion, and chronic inflammation coupled with the acute inflammatory reaction caused by SARS-CoV-2 resulting in a propensity for inflammatory storm.\[179\] \[180\]

### chronic respiratory disease

• People with chronic lung diseases such as chronic obstructive pulmonary disease (COPD), interstitial lung disease, pulmonary embolism, pulmonary hypertension, tuberculosis, cystic fibrosis, and bronchiectasis are at increased risk for severe disease. People with asthma, bronchopulmonary dysplasia, and alpha-1 antitrypsin deficiency may be at increased risk for severe disease; however, evidence is limited.\[146\] There is no clear evidence that people with asthma or COPD are at higher risk of infection.\[181\] \[182\]

• COPD: associated with an increased risk of hospitalization, intensive care unit admission, and mortality.\[183\] A national, multicenter prospective cohort study in the UK found that patients with COPD were less likely to receive critical care than patients without an underlying respiratory condition.\[184\]

• Asthma: associated with similar (if not slightly improved) clinical outcomes compared with those without asthma. Pooled results from a large systematic review showed that, overall, asthma was not associated with severe outcomes (hospitalization, intensive care unit admission, mortality). However, evidence was of very low certainty, and results were limited by a lack of reporting on asthma severity, unexplained statistical heterogeneity, and imprecision. People with allergic asthma appear to be at a lower risk of severe outcomes, while people with asthma and concurrent COPD appear to be at a high risk of severe outcomes. Previous systematic reviews and meta-analyses have generated conflicting conclusions. Whether asthma is associated with an increased risk of infection or severe outcomes remains unclear.\[185\] \[186\]

• Obstructive sleep apnea: associated with an increased risk for severe disease, intensive care admission, mechanical ventilation, and mortality, but not an increased risk of infection; however, evidence is limited.\[187\] \[188\]

• Cystic fibrosis: does not appear to be associated with an increased risk of infection; however, there is evidence that some patients may experience a more severe clinical course (e.g., post-transplantation).\[189\]

• Active pulmonary tuberculosis: appears to be associated with an increased risk of severe disease and mortality.\[190\] \[191\]

• Interstitial lung disease: appears to be associated with an increased risk of severe disease and mortality.\[192\]

• There are no data on whether pediatric respiratory diseases (including childhood asthma) are risk factors for infection or severity.\[193\]

### chronic kidney disease

• People with chronic kidney disease are at increased risk for severe disease, and may be at higher risk for infection.\[129\] \[146\]
• Patients with chronic kidney disease had a significantly higher risk of hospitalization and all-cause mortality compared with people without chronic kidney disease. Patients with chronic kidney disease also had a higher risk of progressing to critical illness in the pooled analysis of included studies and subgroup analyses of studies with multivariable adjustment, although neither result achieved statistical significance.[194]

• Incidence appears to be higher in patients receiving dialysis compared with those not requiring renal replacement therapy.[195] Patients with end-stage renal disease who were on renal replacement therapy also had an increased risk of intensive care unit admission, need for mechanical ventilation, and mortality.[196]

• In the UK, data from a cross-sectional study found that the adjusted odds of a positive test were greater in patients with chronic kidney disease (32.9%) compared with those without (14.4%).[129]

• Preexisting chronic kidney disease is an independent risk factor for developing acute kidney injury as a complication.[197]

chronic liver disease

• People with chronic liver disease such as cirrhosis, metabolic dysfunction-associated fatty liver disease, alcoholic liver disease, and autoimmune hepatitis are at increased risk for severe disease. People with hepatitis B or C may be at increased risk for severe disease; however, evidence is limited.[146]

• Chronic liver disease has been associated with an increased risk for severe disease and mortality, but not an increased risk of infection.[198] Higher liver fibrosis scores are associated with worse prognosis.[199]

• People with cirrhosis are at an increased risk of mortality. Cirrhotic patients had a 2.48-fold increased odds of mortality compared with noncirrhotic patients. Mortality risk is potentially higher in patients with more advanced cirrhosis.[200]

• People with metabolic dysfunction-associated fatty liver disease (nonalcoholic fatty liver disease) are at increased risk for severe disease.[201] Disease severity has been associated with age <60 years and intermediate or high fibrosis-4 (FIB-4) scores.[202][203]

pregnancy

• Pregnant women are at increased risk for severe disease.[146]

• According to an analysis of approximately 400,000 women ages 15 to 44 years with symptomatic disease, pregnant women were more likely to be hospitalized, be admitted to the intensive care unit, receive invasive mechanical ventilation or extracorporeal membrane oxygenation, and die compared with nonpregnant women.[40]

• Pregnant women with severe infection were more likely to have a preterm birth or pre-labor cesarean birth, or have a baby that was stillborn or require admission to a neonatal intensive care unit. Risk factors for pregnant women developing severe disease included age ≥30 years, gestational diabetes, overweight/obesity, and mixed ethnicity.[204]

• Pregnant women and neonates are more vulnerable to adverse outcomes in low- to middle-income countries compared with high-income countries.[205]

• See the Complications section for more information on pregnancy-related complications.

smoking

• People who are current or former smokers are at increased risk for severe disease.[146]

• Smoking is associated with severe or critical outcomes, and an increased risk of intensive care unit admission and mortality. The association appears to be more significant in former smokers compared
with current smokers, and in younger people. Current smokers are at higher risk of developing severe disease compared with nonsmokers.[206] [207] Smokers have double the mortality risk compared with nonsmokers.[208] This may be due to increased airway expression of the angiotensin-converting enzyme-2 receptor in smokers.[209] The risk of mortality in current smokers does not appear to vary by age; however, the risk drops significantly by age in former smokers.[210]

- The World Health Organization has reviewed the available evidence and concluded that smoking is associated with increased severity of disease and death in hospitalized patients.[211]

**malignancy**

- People with cancer are at increased risk for infection and severe disease.[146] [212]
- Patients with cancer have an increased risk of severe disease, increased ventilatory requirements, and mortality compared with the general population. Intensive care unit admission rates were not statistically significant between the two groups. Hematologic malignancies were associated with the highest risk of severe disease and mortality (possibly explained by the greater degree of immunosuppression used in the treatment of these patients), followed by lung cancer. There is no clear association between treatment modality and mortality. A higher risk of infection is likely due to immunosuppressive treatments and/or recurrent hospital visits.[213] [214]
- The pooled in-hospital mortality risk in patients with cancer is 14.1%.[215] The pooled mortality in cancer patients admitted to the intensive care unit is 60.2%.[216] Mortality in cancer patients is affected by preexisting noncancer comorbidities, and is significantly higher in people with hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and diabetes.[217] A registry-based study suggests that mortality in patients with cancer has improved over time in Europe, and this improvement may be associated with earlier diagnosis, improved clinical management, and changes in community transmission over time.[218]
- Patients with recent cancer treatment (within 3 months before COVID-19 diagnosis) had a statistically significant increase in the risk of 30-day mortality, intensive care unit stay, and hospitalization compared with patients with COVID-19 without cancer. Patients with no recent cancer treatment had a similar risk of mortality and intensive care unit stay, and a lower risk of mechanical ventilation and hospitalization compared with patients without cancer.[219]
- Children with cancer may be no more vulnerable to infection compared with children without cancer. Limited data show that the overall morbidity in pediatric patients with cancer is low, with only 5% requiring hospitalization for symptoms.[220] In the largest international cohort study to date, 20% of children with cancer developed severe or critical disease, but most patients recovered without advanced support. Approximately 35% of children were asymptomatic. Lymphopenia and neutropenia were associated with more severe disease.[221] Overall survival in children with cancer is very high (99.4%), and there was no significant difference in the risk of hospitalization or intensive care unit admission between hematologic malignancies and solid tumors in children.[222] Limited evidence suggests that no severe complications were associated with continuation of chemotherapy in children who test positive for SARS-CoV-2.[223]

**cerebrovascular disease**

- People with cerebrovascular disease are at increased risk for severe disease.[146]
- Patients with a history of cerebrovascular disease were more likely to progress to adverse outcomes compared with patients without a history of cerebrovascular disease.[224] Patients with preexisting cerebrovascular disease had 2.67-fold higher odds of poor outcomes including intensive care admission, mechanical ventilation, and mortality.[225]
mental health disorders

- People with mental health disorders such as mood disorders (e.g., depression) and schizophrenia-spectrum disorders are at increased risk for severe disease.[146]
- People with preexisting mental health disorders have an increased risk of hospitalization and mortality compared with patients without mental health disorders.[226] [227]
- People with preexisting schizophrenia may be at increased risk of mortality. Risk factors include older age and a history of smoking.[228]

solid organ or blood stem cell transplant

- People with an immunocompromised state from solid organ or blood stem cell transplant are at increased risk for severe disease.[146]
- Solid organ transplant recipients are at increased risk for hospitalization, intensive care unit admission, and mortality. However, the increased rate of hospitalization may reflect a preferred management strategy of closer inpatient monitoring in these patients rather than being an indicator of disease severity. No increased risk in mortality was found compared with the general population when adjusted for demographic and clinical features and disease severity.[229]
- Hematopoietic stem cell transplant (HSCT) recipients are at increased risk for mortality. The mortality rate was slightly higher in allo-HSCT recipients compared with auto-HSCT recipients, but this difference was not statistically significant. Risk factors for higher mortality included older age, immunosuppressive therapy, graft-versus-host disease, and elevated inflammatory markers with lymphopenia.[230]

disabilities

- People with disabilities including Down syndrome, cerebral palsy, congenital malformations, learning disabilities, attention deficit/hyperactivity disorder, intellectual and developmental disabilities, and spinal cord injuries are at increased risk for severe disease.[146]
- In the UK, a cohort study found a 4-fold increased risk for hospitalization and a 10-fold increased risk for mortality in people with Down syndrome.[231] This may possibly be due to the presence of immune dysfunction, congenital heart disease, and pulmonary pathology.
- Another study in the UK found that adults with learning disability and those with Down syndrome or cerebral palsy have markedly increased risks of hospital admission and death over and above the risks observed for non-COVID-19 causes of death.[232]
- The risk of death was higher for disabled people (including learning disability, neurologic conditions, and frailty) compared with nondisabled people during the first two waves of the pandemic. Relative risks were high among younger disabled people, disabled women, and people with greater levels of activity limitation. Adverse socioeconomic, demographic, and health-related risk factors accounted for some of the elevated risk.[233]

dementia

- People with dementia may be at increased risk for infection and are at increased risk for severe disease.[146] [234]
- Older adults with dementia are at a higher risk of mortality in the short term. Dementia patients are more likely to be vulnerable to having diseases such as hypertension, diabetes, and pneumonia, and be immunocompromised. The pooled mortality rate of patients with dementia was 39% compared with 20% in older adults without dementia.[235]
• In the UK, over one quarter of people who died with COVID-19 from March to June 2020 had dementia. Dementia and Alzheimer disease was the most common main preexisting health condition in deaths involving COVID-19 between March and June 2020.[236]

• A retrospective case-control study of electronic patient health records in the US found that patients with dementia were at increased risk of infection compared with patients without dementia. They also had significantly worse outcomes (6-month hospitalization risk and mortality risk) compared with patients with dementia but no COVID-19 and patients with COVID-19 but no dementia. The highest risk was seen in patients with vascular dementia.[237]

**immunosuppression**

• People who are immunocompromised are at increased risk for severe disease.[146]

• This includes people with a history of primary immune deficiencies or prolonged use of corticosteroids or other immunosuppressant medications.

• Current data do not strongly suggest that medications associated with the treatment of immune-mediated inflammatory diseases increase the risk of infection or severe disease, with the exception of corticosteroids and rituximab.[238]

• Glucocorticoid exposure of ≥10 mg/day (prednisone) has been associated with a higher odds of hospitalization in patients with rheumatologic disease.[239] Patients treated with cyclosporine/tacrolimus also had an increased risk for hospitalization; however, it was not clear whether the increased risk is related to the drug itself, the underlying condition for which the patient is treated, or other factors.[240]

• Immunosuppressed patients are not at significantly increased risk of infection compared with the general population.[241]

• Also see HIV infection and Autoimmune disease below.

**HIV infection**

• People living with HIV are at increased risk for severe disease.[146]

• Retrospective studies have found that while people with HIV do not appear to be at increased risk of infection, they are at increased risk for poor outcomes (i.e., severe disease, hospitalization, mortality) compared with people living without HIV infection. The risk of severe disease and hospitalization increased with progression of HIV disease stage.[242] [243] [244] [245] However, there is some evidence that suggests that HIV patients at advanced stages (stage 3 or 4) may manifest less severe symptoms and have reduced mortality. This may be due to the inability of HIV-positive individuals' immune systems to provoke the cytokine storm that usually causes poor clinical outcomes in COVID-19 patients.[246]

• Evidence from meta-analyses is conflicting. One meta-analysis found that HIV infection was not associated with composite poor outcome.[247] However, other meta-analyses have found that people living with HIV infection have an increased risk for infection and mortality compared with people without HIV. People on tenofovir disoproxil-based regimens may have a lower risk of infection and poor outcomes; however, evidence is inconclusive.[248] [249] [250] [251]

• The World Health Organization states that HIV infection appears to be a significant independent risk factor for severe or critical disease at hospital admission and in-hospital mortality. HIV infection was independently associated with a higher risk of mortality compared with the HIV-negative population after adjusting for age, sex, disease severity, and underlying conditions. Age >65 years, male sex, and the presence of diabetes or hypertension were risk factors for severe or critical illness at hospital admission, as well as in-hospital mortality. Data were predominantly from South Africa, which may
limit the generalizability of the results.[252] Other risk factors for severe illness include coexisting cardiovascular disease, respiratory disease, and chronic kidney disease.[253]

hemoglobin disorders

- People with sickle cell disease or thalassemia may be at increased risk for severe disease; however, evidence is limited.[146]
- Patients with hemoglobinopathy had an increased risk of severe disease and mortality compared with the general population. Mortality among patients with hemoglobinopathy was 6.9%. Respiratory and cardiovascular comorbidities were significant predictors of mortality.[254]
- In the UK, patients with sickle cell disease were found to have a 4-fold increased risk for hospitalization and a 2.6-fold increased risk for death. Sickle cell trait was also associated with increased risks for both outcomes, albeit to a lesser extent.[255]
- In the US, among 178 patients with sickle cell disease (mean patient age <40 years), 69% were hospitalized, 11% were admitted to intensive care, and 7% died.[256] Infection can cause acute chest syndrome in patients with sickle cell disease.[257] [258]

hypertension

- People with hypertension may be at increased risk for severe disease; however, evidence is limited.[146]
- Almost all available evidence suggests that hypertension increases the risk of severe disease or mortality, although it was sometimes unclear whether this was independent of other risk factors. There were no systematic reviews or meta-analyses studying whether people with hypertension were at greater risk of infection.[259] [260]
- Hypertension has been associated with increased poor composite outcome, including mortality, severe disease, acute respiratory distress syndrome, need for intensive care admission, and disease progression.[261] Patients with hypertension have a 2.98-fold higher risk of severe disease, a 1.82-fold higher risk of critical disease, and a 2.17 to 2.88-fold higher risk of fatality compared with patients without hypertension.[262] [263]
- Initially, there was a concern that people on ACE inhibitors or angiotensin-II receptor antagonists may be at increased risk for infection or severe disease due to upregulation of ACE2 receptor expression.[264] However, high-certainty evidence suggests that use of these drugs is not associated with severe disease, and there is no association between the use of these medications and a positive SARS-CoV-2 test result among symptomatic patients.[265] [266]

substance use disorders

- People with substance use disorders may be at increased risk for severe disease; however, evidence is limited.[146] This includes alcohol, opioid, or cocaine use disorder.
- People with substance abuse disorders, especially those using drugs that affect the respiratory and cardiovascular systems, may be vulnerable to the adverse respiratory effects of COVID-19. Cohort studies have found substance use disorders were associated with increased hospitalization, intensive care unit admission, ventilator use, and mortality.[267] [268]
- People with opioid use disorder had higher odds of hospitalization, maximum length of hospital stay, and invasive mechanical ventilation compared with those without an opioid use disorder. However, patients did not appear to have an increased risk of mortality. Patients treated with methadone or buprenorphine appeared to have worse outcomes in terms of hospitalization and length of hospital stay, but better outcomes in terms of mortality risk and need for invasive mechanical ventilation compared with patients not receiving opioid agonist treatment.[269]
children with certain underlying conditions

- Children with certain underlying conditions may be at increased risk for severe disease; however, evidence is limited.[146]
- These conditions include obesity, diabetes, asthma and chronic lung disease, immunosuppression, and sickle cell disease. Children may also be at risk if they are medically complex; have serious genetic, neurologic, or metabolic disorders; or have congenital heart disease.[146]
- A cross-sectional study of over 43,000 children in the US found that the most commonly documented underlying conditions were obesity, asthma, neurodevelopmental disorders, anxiety and fear-related disorders, and depressive disorders. Children with type 1 diabetes, cardiac and circulatory congenital anomalies, obesity, hypertension, epilepsy, neuropsychiatric disorders, and asthma as well as children with chronic disease had higher risk of hospitalization and severe disease. Limited data suggest that children with congenital heart disease might be at increased risk of severe disease.[270]

Weak

vitamin D deficiency

- People with vitamin D deficiency may be at higher risk for infection and severe disease; however, evidence is limited.
- Meta-analyses have found that low serum vitamin D level is significantly associated with a higher risk of infection, and increased risk for severe disease, hospitalization, and mortality in both adults and children.[271] [272] [273] [274] [275] [276] [277] However, it is unclear whether these associations were statistically significant and the certainty of evidence is very low.[278] [279]
- A meta-analysis and GRADE assessment of cohort studies and randomized controlled trials found that current evidence suggests that vitamin D deficiency is not significantly linked to susceptibility to infection or death, and vitamin D supplementation did not significantly improve clinical outcomes. However, the overall quality of evidence was low.[280]

proton-pump inhibitor use

- People taking proton-pump inhibitors (PPIs) may be at increased risk for infection and severe disease; however, evidence is limited.[281]
- Data on whether PPI use increases the risk for infection is conflicting. The largest meta-analysis to date found that PPI use was marginally associated with a nominal, but statistically significant, increase in the risk of infection, as well as an increased risk of severe infection and mortality.[281]
- Current or regular users of PPIs were more likely to have severe outcomes compared with non-PPI users. Also, current PPI users were more likely to be hospitalized for longer compared with non-PPI users, although this was not statistically significant. Past use of PPIs is not associated with increased susceptibility to infection or severe outcomes.[282]

autoimmune disease

- People with autoimmune disease (including rheumatic and musculoskeletal diseases) may be at higher risk for infection and severe disease; however, evidence is limited.[283] [284]
- Current data do not strongly suggest that the presence of an immune-mediated inflammatory disease increases the risk of infection or severe disease. The increased risk reported in some studies may be due to comorbidities associated with immune-mediated inflammatory diseases or medications the patient is taking (corticosteroids, rituximab). Increased rates of hospitalization in these patients were not associated with increased rates of death.[238] Tumor necrosis factor (TNF)-alpha inhibitor monotherapy was associated with a lower risk of hospitalization or death among patients with immune-
Coronavirus disease 2019 (COVID-19) Diagnosis

mediated inflammatory disorders compared with other treatment regimens (e.g., methotrexate, azathioprine, Janus kinase inhibitors).[285] There was no increased risk of mechanical ventilation or in-hospital mortality for other rheumatologic, antineoplastic, or antimetabolite therapies examined in one cohort study, with the exception of rituximab.[286]

- Inflammatory arthritis: evidence does not show a strong association between inflammatory arthritis (e.g., rheumatoid arthritis, spondyloarthritis) and risk of infection or adverse outcomes such as hospitalization, intensive care unit admission, need for mechanical ventilation, or death. However, evidence is conflicting. Some studies do report an increased risk of adverse outcomes, but the studies had limitations.[238]

- Inflammatory bowel disease: prevalence in patients with inflammatory bowel disease appears to be low.[287] Evidence suggests that the risk profile for infection and severe disease is similar to the general population if patients have good disease control and do not use corticosteroids.[238] Corticosteroid use was associated with an increased risk for severe disease and intensive care unit admission, but not mortality.[288] One third of patients with inflammatory bowel disease required hospitalization, and fewer than 4% required intensive care unit admission.[287] Higher disease activity and flares may lead to increased susceptibility to infection and worse outcomes.[289] Patient outcomes (hospitalization, intensive care unit admission, and mortality) were worse in ulcerative colitis and patients on corticosteroids, thiopurines, aminosalicylates, or combination therapy. Outcomes were better in patients on biologic agents.[287] [290] [291] [292] A risk calculator has been developed that predicts which patients with inflammatory bowel disease are at higher risk of adverse outcomes.[293]

- Connective tissue diseases: several studies suggest an increased risk of infection in patients with connective tissue disorders (e.g., systemic lupus erythematosus, Sjogren syndrome, systemic sclerosis, polymyositis and dermatomyositis) compared with the general population and patients with other immune-mediated inflammatory diseases. This is possibly due to the widespread use of corticosteroids in these patients. There are a lack of data regarding outcomes and evidence is conflicting.[238] Patients with lupus nephritis were at increased risk of developing severe or critical disease.[294]

- Psoriasis: data on risk and outcomes convincingly suggest a comparable risk profile as observed in the general population, with no increase in susceptibility to infection or severe disease reported in cohort studies.[238]

- Vasculitis: corticosteroid use, older age, male sex, moderate or severe disease activity, comorbidities (e.g., respiratory disease), and rituximab or cyclophosphamide use were associated with severe outcomes, based on limited data.[295] [296]

- Multiple sclerosis: neurologic disability, older age, Black race, cardiovascular comorbidities, recent treatment with corticosteroids, and obesity were risk factors for severe disease and mortality.[297] [298] Current evidence does not suggest that multiple sclerosis significantly increases the mortality rate. Highest hospitalization and mortality rates were in patients who were not on disease-modifying therapies, followed by those who were on B cell-depleting therapies (e.g., rituximab, ocrelizumab).[299]

**thyroid disease**

- People with hypothyroidism may be at higher risk of severe disease; however, evidence is limited.[300] [301]

- Thyroid disorders (hypothyroidism and unspecified thyroid abnormalities, but not hyperthyroidism) are associated with a higher risk of poor outcomes including severe disease, hospitalization, intensive care unit admission, and mortality. This association was significantly associated with increasing age and presence of hypertension.[302] [303]
**Parkinson disease**

- People with Parkinson disease may be at higher risk for infection or severe disease; however, evidence is limited.[304] [305] [306]
- Risk factors for infection may include obesity, pulmonary disease, and hospitalization. Vitamin D supplementation was associated with a lower risk of infection.[305]
- Parkinson disease was associated with severe disease, poor in-hospital outcomes, and mortality in one meta-analysis. However, the evidence for an association is still unclear. The association was influenced by age, but not by sex or the presence of dementia, hypertension, or diabetes.[304]
- Patients may experience substantial worsening of parkinsonian symptoms.[307]

**physical inactivity**

- Physical inactivity may be associated with a higher risk for severe disease; however, evidence is limited.[308]
- A retrospective observational study in nearly 50,000 patients found that patients with COVID-19 who were consistently inactive during the 2 years before the pandemic had a greater risk of hospitalization, intensive care unit admission, and death compared with patients who were consistently meeting physical activity guidelines or who were doing some level of physical activity. Other than older age and a history of organ transplant, physical inactivity was the strongest risk factor for severe disease outcomes in this study.[309]

**gout**

- Gout appears to be associated with an increased risk for infection and mortality; however, evidence is limited.[310]
- A UK Biobank population-based study of over 15,000 people with gout found that gout was associated with an increased risk for diagnosis of COVID-19 and COVID-19-related death, independent of the metabolic comorbidities of gout. Women were at a higher risk of death compared with men. There were no significant differences in the risk of COVID-19-related death according to prescription of colchicine or urate-lowering therapy.[310] Evidence is limited and further research is required.

**dyslipidemia**

- Dyslipidemia appears to be associated with an increased risk for severe disease and mortality; however, evidence is limited.[311] [312] [313]
- The association was stronger in males, older age, and those with hypertension.[314]
- Initially there was a concern that people on statins may be at increased risk of infection or more severe disease, as statins have been shown to increase ACE2 expression in animals and may promote the activation of the inflammatory pathway in acute respiratory distress syndrome.[264] However, so far, studies do not support this hypothesis, and studies have shown a protective effect (lower risk of mortality or severe disease).[315] Findings from the American Heart Association’s COVID-19 Cardiovascular Disease Registry report that patients taking statins prior to hospitalization had substantially lower odds of death, primarily among individuals with a history of cardiovascular disease and/or hypertension.[316] Similar findings have been reported from a Swedish registry study.[317]

**surgery**

- Surgical mortality and complications may be higher in patients with COVID-19 compared with patients without COVID-19.[318]
• A retrospective study of 34 patients in China who underwent elective surgeries during the incubation period of COVID-19 found that all patients developed pneumonia after surgery. Approximately 44% of these patients required admission to the intensive care unit, and 20% died.[319]
• Postoperative pulmonary complications occur in half of patients with perioperative SARS-CoV-2 infection, and are associated with higher mortality, particularly in men and those ages 70 years and over.[320]

**blood groups A and B**

• People with blood group A may be at increased risk for infection and mortality, and people with blood groups B and AB may be at increased risk for infection; however, evidence is limited.[321] [322] [323]
• Blood group O appears to be protective against infection; however, evidence is of low/very low quality. People who are Rh-positive were more vulnerable to infection compared with those who were Rh-negative.[321] [324]
• A genome-wide association study found that patients with blood group A are at 45% increased risk of respiratory failure compared with other blood groups. It also found a protective effect in blood group O. Two chromosomal loci were associated with respiratory failure, and one of these coincided with the ABO blood group locus.[120] The SARS-CoV-2 receptor-binding domain directly binds the blood group A antigen expressed on respiratory epithelial cells, directly linking blood group A and SARS-CoV-2.[325]

**gut dysbiosis**

• There is limited evidence that gut and lung microbiota dysfunction may be implicated in the pathogenesis of COVID-19.[326]
• Patients appear to have a depletion of beneficial commensals (e.g., *Eubacterium ventriosum*, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *Roseburia* and Lachnospiraceae taxa) and an overgrowth of opportunistic pathogens (e.g., *Clostridium hathewayi*, *Actinomyces viscosus*, *Bacteroides nordii*) during hospitalization.[327] [328] [329] Associations between gut microbiota composition, levels of cytokines, and inflammatory markers in patients with COVID-19 suggest that the gut microbiome is involved in disease severity, possibly via modulating host immune responses. Gut dysbiosis after disease resolution may contribute to persistent symptoms.[330]

**environmental factors**

• Climate and latitude: higher temperatures may slow the progression of the epidemic based on low-certainty evidence and limited studies; however, climate variables alone don’t explain most of the variability in disease transmission. Temperature, humidity, wind speed, ultraviolet light, and latitude may play a role in the epidemic, but further research is required.[331]
• Air pollution: limited evidence suggests an association between exposure to ambient air pollution and COVID-19; however, evidence is not sufficient to prove causation.[332] [333] [334] [335] [336]
• Residence in urban or deprived areas: limited evidence suggests that the prevalence was greater in people living in urban areas compared with people living in rural areas, and in people living in more deprived areas compared with people living in less deprived areas.[129] [337]
# Investigations

## 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>real-time reverse transcription polymerase chain reaction (RT-PCR)</td>
<td>positive for SARS-CoV-2 viral RNA; may be positive for influenza A and B viruses and other respiratory pathogens</td>
</tr>
</tbody>
</table>

- Order an RT-PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with suspected infection whenever possible.\[^{539}\] Testing strategies vary widely between countries.
- Commonly used assays are expected to be able to detect SARS-CoV-2 variants. However, some tests may be impacted by variants.\[^{580}\] The US Food and Drug Administration has warned that false-negative results may occur with any molecular test for the detection of SARS-CoV-2 if a mutation occurs in the part of the virus' genome assessed by that test. Multiple genetic targets to determine a final result are less likely to be impacted by increased prevalence of genetic variants. Consider negative results in combination with clinical observations, patient history, and epidemiologic information.\[^{725}\]
- Molecular testing is an aid to diagnosis only. The World Health Organization recommends that healthcare providers consider a positive or negative result in combination with specimen type, clinical observations, patient history, and epidemiologic information. Where a test result does not correspond with the clinical presentation, a new specimen should be taken and retested using the same or a different molecular test.\[^{579}\]
- Base decisions about who to test on clinical and epidemiologic factors.\[^{539}\] Consult local health authorities for guidance as testing priorities depend on local recommendations and available resources.
- The World Health Organization recommends testing all people who meet the suspected case definition of COVID-19, regardless of vaccination status or disease history. When resources are constrained, people who are at risk of developing severe disease, healthcare workers, inpatients, and the first symptomatic individuals in the setting of a suspected outbreak should be prioritized. Testing of asymptomatic individuals is currently recommended only for specific groups including contacts of confirmed or probable cases and frequently exposed groups such as healthcare workers and long-term care facility workers.\[^{581}\]
- In England, testing symptomatic people is no longer required. Guidance and eligibility for testing varies between the nations of the UK, and you should check your local guidelines. In England, testing is still recommended in the following groups: patients in a hospital setting with symptoms or suspicion of COVID-19 to support a diagnostic pathway, for asymptomatic screening, testing on discharge to certain settings, and in patients with severe immunocompromise; patients on admission in unplanned care settings or preadmission in elective care settings; patients in the community at high risk of complications who are eligible for COVID-19 antivirals and other treatments, or where a clinician requires a test to support clinical decisions in their care; and staff in health and social care settings for asymptomatic screening or if they develop symptoms.\[^{582} \][^{583}]
- In the US, testing is recommended in: (1) anyone with signs or symptoms consistent with COVID-19 (regardless of vaccination status); (2) asymptomatic people with recent known or suspected
Coronavirus disease 2019 (COVID-19)

Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
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<tbody>
<tr>
<td>exposure to SARS-CoV-2, including those who have been in close contact (less than 6 feet [2 meters] for a total of 15 minutes or more over a 24-hour period) with a person with documented infection; (3) asymptomatic people without recent known or suspected exposure to SARS-CoV-2 for early identification, isolation, and disease prevention (only when screening testing is recommended by public health officials). [584]</td>
<td>• The optimal specimen for testing depends on the clinical presentation and the time since symptom onset. The World Health Organization recommends upper respiratory specimens (nasopharyngeal and/or oropharyngeal swabs) for early-stage infections, especially asymptomatic or mild cases, and lower respiratory specimens (sputum and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease) for later-stage infections or patients in whom there is a strong suspicion for infection and their upper respiratory tract specimen test was negative. Other specimens (e.g., nasal mid-turbinate swab, anterior nares swab, nasopharyngeal/nasal wash/aspirate, saliva, fecal) may be recommended in some circumstances; consult local guidance. [539] [726] [592]</td>
</tr>
<tr>
<td>• A positive RT-PCR result confirms SARS-CoV-2 infection (in the context of the limitations associated with RT-PCR testing). If the result is negative, and there is still a clinical suspicion of infection (e.g., an epidemiologic link, typical x-ray findings, absence of another etiology), resample the patient and repeat the test. A positive result confirms infection. If the second test is negative, consider serologic testing (see below). [539]</td>
<td>• A positive RT-PCR result confirms SARS-CoV-2 infection (in the context of the limitations associated with RT-PCR testing). If the result is negative, and there is still a clinical suspicion of infection (e.g., an epidemiologic link, typical x-ray findings, absence of another etiology), resample the patient and repeat the test. A positive result confirms infection. If the second test is negative, consider serologic testing (see below). [539]</td>
</tr>
<tr>
<td>• The pooled sensitivity has been estimated to be 87.8%, with the specificity estimated to be in the range of 87.7% to 100%. [599]</td>
<td>• The pooled sensitivity has been estimated to be 87.8%, with the specificity estimated to be in the range of 87.7% to 100%. [599]</td>
</tr>
<tr>
<td>• Interpret test results with caution. Evidence for the use of RT-PCR in the diagnosis of COVID-19 is still emerging, and uncertainties about its efficacy and accuracy remain. [599] It is not fully understood whether a positive result always represents infectious virus, especially at high cycle thresholds. [600] [601] [603] [604] Interpreting the result depends on the accuracy of the test itself, and the pre- and post-test probabilities of disease. [602] When the pretest probability is low, positive results should be interpreted with caution, and ideally a second specimen tested for confirmation. [605] The lower the prevalence of disease in a given population, the lower the post-test probability. [606] False-positive results can be caused by a laboratory error or a cross-reaction with antibodies formed by current and past exposure to seasonal human coronavirus infections (e.g., common cold), and are more likely when the prevalence of disease is moderate to low. [608] Preliminary estimates of the false-positive rate in the UK are in the range of 0.8% to 4%. [610] False-negative rates of between 2% and 29% have been reported. [602] A systematic review found that the false-negative rate varied across studies from 1.8% to 58% (median 11%); however, there was substantial and largely unexplained heterogeneity across studies. [611]</td>
<td></td>
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<tr>
<td>• Rapid molecular tests are available. They may be suitable for some testing scenarios (e.g., where obtaining test results within 2 hours will enable appropriate decision-making); however, evidence is limited. [625]</td>
<td>• Rapid molecular tests are available. They may be suitable for some testing scenarios (e.g., where obtaining test results within 2 hours will enable appropriate decision-making); however, evidence is limited. [625]</td>
</tr>
<tr>
<td>• Also collect nasopharyngeal swabs to rule out influenza and other respiratory infections according to local guidance. It is important to note that coinfections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19. [87]</td>
<td>• Also collect nasopharyngeal swabs to rule out influenza and other respiratory infections according to local guidance. It is important to note that coinfections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19. [87]</td>
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<tr>
<td>Test</td>
<td>Result</td>
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<tr>
<td>• Single-test multiplex assays to diagnose and differentiate between infection caused by influenza A, influenza B, respiratory syncytial virus, and SARS-CoV-2 are available in some countries.</td>
<td></td>
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<tr>
<td>pulse oximetry</td>
<td>may show low oxygen saturation (cut-off depends on local guidelines)</td>
</tr>
<tr>
<td>• Pulse oximetry may reveal low oxygen saturation. The UK National Institute for Health and Care Excellence recommends using oxygen saturation levels below 94% for adults (or below 88% for adults with known type 2 respiratory failure) and below 91% for children in room air at rest to identify people who are seriously ill.[20]</td>
<td></td>
</tr>
<tr>
<td>• Clinicians should be aware that patients with COVID-19 can develop &quot;silent hypoxia&quot;: their oxygen saturations can drop to low levels and precipitate acute respiratory failure without the presence of obvious symptoms of respiratory distress.[568]</td>
<td></td>
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<tr>
<td>• Pulse oximetry may be available as part of remote monitoring in the community. Evidence suggests that patients who may benefit most from monitoring are those who are symptomatic and are either over 65 years of age, or are under 65 years years of age and are extremely clinically vulnerable to COVID-19. [NHS England: pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings] (<a href="https://www.england.nhs.uk/coronavirus/publication/pulse-oximetry-to-detect-early-deterioration-of-patients-with-covid-19-in-primary-and-community-care-settings">https://www.england.nhs.uk/coronavirus/publication/pulse-oximetry-to-detect-early-deterioration-of-patients-with-covid-19-in-primary-and-community-care-settings</a>)</td>
<td></td>
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<tr>
<td>• Pulse oximeters may exhibit suboptimal accuracy in certain populations. Limited data from studies with small numbers of participants suggest that skin pigmentation can affect pulse oximeter accuracy. In one study, occult hypoxemia (defined in the study as arterial oxygen saturation &lt;88% by arterial blood gas despite oxygen saturation of 92% to 96% on pulse oximetry) was not detected by pulse oximetry nearly three times more frequently in Black patients compared with White patients.[544] The US Food and Drug Administration (FDA) has warned that multiple factors can affect the accuracy of a pulse oximeter reading (e.g., poor circulation, skin pigmentation, skin thickness, skin temperature, current tobacco use, use of fingernail polish). The FDA recommends considering accuracy limitations when using a pulse oximeter to assist in diagnosis and treatment decisions, and to use trends in readings over time rather than absolute cut-offs if possible.[569]</td>
<td></td>
</tr>
<tr>
<td>• Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognizing further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[568]</td>
<td></td>
</tr>
<tr>
<td>• Pulse oximeters can be used at home to detect hypoxia. Home pulse oximetry requires clinical support (e.g., regular phone contact from a health professional in a virtual ward setting).</td>
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<tr>
<td>• [BMJ Practice Pointer: remote management of covid-19 using home pulse oximetry and virtual ward support] (<a href="https://www.bmj.com/content/372/bmj.n677">https://www.bmj.com/content/372/bmj.n677</a>)</td>
<td></td>
</tr>
<tr>
<td>ABG</td>
<td>may show low partial oxygen pressure</td>
</tr>
<tr>
<td>• Order in patients with severe illness as indicated to detect hypercarbia or acidosis.</td>
<td></td>
</tr>
<tr>
<td>• Recommended in patients with respiratory distress and cyanosis who have low oxygen saturation (SpO₂ &lt;90%).</td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>lymphopenia; leukocytosis; leukopenia;</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td>Test</td>
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</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td>thrombocytopenia; decreased eosinophils; decreased hemoglobin</td>
</tr>
<tr>
<td>• Lymphopenia, leukocytosis, thrombocytopenia, decreased eosinophils, decreased hemoglobin, and high neutrophil-to-lymphocyte ratio are significantly associated with severe disease, and may be useful for predicting disease progression. Severe cases are more likely to present with lymphopenia and thrombocytopenia, but not leukopenia.[727]</td>
<td></td>
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<tr>
<td>• Anemia is common and may be associated with a higher risk of mortality.[728]</td>
<td></td>
</tr>
<tr>
<td>• Elevated red blood cell distribution width (at admission and increasing during hospitalization) has been associated with a significantly increased risk of mortality in hospitalized patients.[729]</td>
<td></td>
</tr>
<tr>
<td>• Absolute counts of major lymphocyte subsets, particularly CD4+ and CD8+ T-cell counts, are significantly decreased in patients with severe disease.[730]</td>
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<tr>
<td>• Late-phase thrombocytopenia (i.e., occurring 3 weeks or more after symptom onset) has been reported but is uncommon.[731]</td>
<td></td>
</tr>
<tr>
<td>comprehensive metabolic panel</td>
<td>elevated liver enzymes; elevated total bilirubin; renal impairment; hypoalbuminemia; electrolyte derangements</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated liver enzymes, total bilirubin, creatinine, and blood urea nitrogen, and hypoalbuminemia are significantly associated with severe disease, and may be useful for predicting disease progression.[727]</td>
<td></td>
</tr>
<tr>
<td>• Hypokalemia has been reported in 54% of patients.[732] Hypocalcemia has been reported and is associated with poor outcomes.[733] Hyponatremia has been reported in 24% of patients, and is associated with poor outcomes.[734] Other electrolyte derangements may be present.</td>
<td></td>
</tr>
<tr>
<td>thyroid function tests</td>
<td>elevated TSH; low free T3 or T4</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td>variable</td>
</tr>
<tr>
<td>• Most patients had lower triiodothyronine (T3) levels and normal or low thyroid-stimulating hormone (TSH). However, increased TSH ranged from 5.1% to 8%, while low T3 was present in up to 28% of patients. There was significant heterogeneity among studies.[301]</td>
<td></td>
</tr>
<tr>
<td>blood glucose level</td>
<td>elevated D-dimer; prolonged prothrombin time; elevated fibrinogen; prolonged INR</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Fasting hyperglycemia independently predicts poor prognosis and is associated with an increased risk of mortality, regardless of whether or not the patient has diabetes.[735] [736]</td>
<td></td>
</tr>
<tr>
<td>• Hypoglycemia has also been associated with increased mortality in a retrospective cohort study.[737]</td>
<td></td>
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<tr>
<td>coagulation screen</td>
<td></td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated D-dimer, elevated fibrinogen (and fibrin degradation product), and prolonged prothrombin time are significantly associated with severe disease, and may be useful for predicting disease progression.[727] [738]</td>
<td></td>
</tr>
<tr>
<td>• The risk of severe disease and mortality is 2-fold and 4-fold higher, respectively, in patients with elevated D-dimer levels.[739] Patients with very high D-dimer levels have an increased risk of thrombosis.[740] [741]</td>
<td></td>
</tr>
<tr>
<td>• Prolonged international normalized ratio (INR) values have been associated with more severe disease and mortality.[742]</td>
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</table>
### Test

<table>
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<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>• Von Willebrand factor markers may be increased, especially in patients with critical disease, and may have prognostic value.[743]</td>
<td>may be elevated</td>
</tr>
<tr>
<td><strong>cardiac biomarkers</strong></td>
<td><strong>may be elevated</strong></td>
</tr>
</tbody>
</table>
| • Order in patients with severe illness.  
• Elevated creatine kinase-myocardial band (CK-MB), B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), and troponin are associated with severe disease and mortality, and may be useful for predicting disease progression or survival.[744]  
• CK-MB has been found to be elevated in mild disease in children. The significance of this is unknown.[576] |  |
| • Order in patients with severe illness.  
• Elevated creatine kinase-myocardial band (CK-MB), B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), and troponin are associated with severe disease and mortality, and may be useful for predicting disease progression or survival.[744]  
• Patients with elevated C-reactive protein at the time of initial presentation were more likely to have acute kidney injury, venous thromboembolism, critical illness, and in-hospital mortality during their hospital stay compared with patients with lower levels.[746] |  |
| • Order in patients with severe illness.  
• Elevated serum interleukin (IL) level is significantly associated with severe disease, and may be useful for predicting disease progression.[727]  
• Less likely to be elevated in children.[747]  
• Increased serum levels of other interleukin types (e.g., IL-1 beta, IL-1Ra, IL-2R, IL-4, IL-6, IL-8, IL-10, IL-18) have also been associated with severe disease and mortality.[748] |  |
| • Order in patients with severe illness.  
• Elevated serum procalcitonin is significantly associated with severe disease, and may be useful for predicting disease progression.[727]  
• Elevated serum procalcitonin may be more common in children.[749]  
• May be elevated in patients with secondary bacterial infection.[47] [48]  
• There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about the use of antibiotics. However, it may be helpful in identifying whether there is a bacterial infection, although the most appropriate procalcitonin threshold is uncertain.[20] |  |
| • Order in patients with severe illness.  
• Elevated serum ferritin level is significantly associated with severe disease, and may be useful for predicting disease progression.[727]  
• Elevated serum ferritin level may be more common in children.[749]  
• May be elevated in patients with secondary bacterial infection.[47] [48]  
• There is insufficient evidence to recommend routine ferritin testing to guide decisions about the use of antibiotics. However, it may be helpful in identifying whether there is a bacterial infection, although the most appropriate ferritin threshold is uncertain.[20] |  |

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<table>
<thead>
<tr>
<th>Test</th>
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</tr>
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</table>
| • Elevated ferritin is significantly associated with severe disease, and may be useful for predicting disease progression.[750]  
  • May indicate development of cytokine release syndrome.[751] |                                             |
| serum amyloid A level                         | may be elevated                             |
  • Order in patients with severe illness.  
  • Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[752] [753] |
| serum creatine kinase and myoglobin           | may be elevated                             |
  • Order in patients with severe illness.  
  • Elevated serum creatine kinase and myoglobin are significantly associated with severe disease, and may be useful for predicting disease progression.[727] |
| blood and sputum cultures                    | negative for bacterial infection            |
  • Collect blood and sputum specimens for culture in patients with severe or critical disease to rule out other causes of lower respiratory tract infection and sepsis, especially patients with an atypical epidemiologic history.[87]  
  • Specimens should be collected prior to starting empiric antimicrobials if possible. |
| chest x-ray                                   | ground-glass opacity; consolidation         |
  • Order in all patients with suspected pneumonia.  
  • Approximately 74% of patients have an abnormal chest x-ray at the time of diagnosis. The most common abnormalities are ground-glass opacity (29%) and consolidation (28%). Distribution is generally bilateral, peripheral, and basal zone predominant. Pneumothorax and pleural effusions are rare. There is no single feature on chest x-ray that is diagnostic for COVID-19.[634]  
  • Chest x-ray is moderately sensitive and moderately specific for the diagnosis of COVID-19. Pooled results found that chest x-ray correctly diagnosed COVID-19 in 80.6% of people who had the disease. However, it incorrectly identified COVID-19 in 28.5% of people who did not have the disease.[635]  
  • Although chest x-ray appears to have a lower sensitivity compared with chest CT, it has the advantages of being less resource-intensive, associated with lower radiation doses, easier to repeat sequentially, and portable.[636] |
Other tests to consider

<table>
<thead>
<tr>
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<th>Result</th>
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</table>
| computed tomography (CT) chest| - Consider a CT scan of the chest. Consult local guidance on whether to perform a CT scan. The British Society of Thoracic Imaging (BSTI) recommends CT imaging in patients with clinically suspected COVID-19 who are seriously ill if chest x-ray is uncertain or normal. [BSTI: radiology decision tool for suspected COVID-19](https://www.bsti.org.uk/media/resources/files/NHSE_BSTI_APPROVED_Radiology_on_CoVid19_v6_modified1_Read-Only.pdf) Some institutions in the UK recommend a more pragmatic approach for patients with high clinical suspicion of COVID-19, with chest CT recommended only after two indeterminate or normal chest x-rays in combination with a negative RT-PCR test.[638] The American College of Radiology recommends reserving CT for hospitalized, symptomatic patients with specific clinical indications for CT, and emphasizes that a normal chest CT does not mean that a patient does not have COVID-19 and that an abnormal chest CT is not specific for COVID-19 diagnosis.[639]  
- Chest CT is sensitive and moderately specific for the diagnosis of COVID-19. Pooled results found that chest CT correctly diagnosed COVID-19 in 87.9% of people who had the disease. However, it incorrectly identified COVID-19 in 20% of people who did not have the disease. Therefore, chest CT may have more utility for excluding COVID-19 than for differentiating it from other causes of respiratory illness.[635] Accuracy appears to be lower among children; however, there are limited data in this population.[637]  
- Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[640] Some patients may present with a normal chest finding despite a positive RT-PCR.[641] Results of RT-PCR testing may be false-negative, so patients with typical CT findings should have repeat RT-PCR testing to confirm the diagnosis.[642] CT imaging abnormalities may be present in asymptomatic patients. The pooled estimate of the rate of positive chest CT findings in asymptomatic cases was 47.6% (mainly ground-glass opacity).[643]  
- Abnormal chest CT findings have been reported in up to 97% of hospitalized patients.[645] The most common findings are ground-glass opacity, either in isolation or coexisting with other findings such as consolidation, interlobular septal thickening, or crazy-paving pattern. The most common distribution pattern is bilateral, peripheral/subpleural, posterior distribution of the opacities, with a lower lobe predominance. Extensive/multilobar involvement with consolidations is more common in older patients and those with severe disease. Pulmonary vascular enlargement, interlobular or intralobular septal thickening, adjacent pleural thickening, air bronchograms, subpleural lines, crazy-paving pattern, bronchus distortion, bronchiectasis, vascular retraction sign, and halo sign are atypical features. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have also been reported rarely.[646] Ground-glass opacity has the highest diagnostic performance for COVID-19 pneumonia, followed by ground-glass opacity plus consolidation, and consolidation only.[647]  
- Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity, nonspecific patchy shadows, areas of consolidation, infected nodules, ground-glass opacity in isolation or coexisting with other findings (e.g., consolidation, interlobular septal thickening, crazy-paving pattern); bilateral, peripheral/subpleural, posterior distribution with a lower lobe predominance. |
Coronavirus disease 2019 (COVID-19)

**Test**

and a halo sign. Abnormalities are more common in multiple lobes and are predominantly bilateral. Pleural effusion is rare.[650] [754] Ground-glass opacity and peribronchial thickening were the most prevalent findings in infants younger than 1 year of age.[651]

- CT scan generally shows an increase in the size, number, and density of ground-glass opacities in the early follow-up period, with a progression to mixed areas of ground-glass opacities, consolidations, and crazy paving peaking at day 10 to 11, before gradually resolving or persisting as patchy fibrosis.[646]

- The positive predictive value was low (1.5% to 30.7%) in low-prevalence regions, and the negative predictive value ranged from 95.4% to 99.8% in one meta-analysis. Pooled sensitivity and specificity were 94% to 96% and 37%, respectively.[755] [756] The simultaneous presence of ground-glass opacity and other features of viral pneumonia had optimum performance in the detection of COVID-19 (sensitivity 90% and specificity 89%).[648]

- CT is more sensitive than RT-PCR in detecting COVID-19, but has a very low specificity.[757] In a cohort of over 1000 patients in a hyperendemic area in China, chest CT had a higher sensitivity for diagnosis of COVID-19 compared with initial RT-PCR from swab samples (88% versus 59%). Improvement of abnormal CT findings also preceded change from RT-PCR positivity to negativity in this cohort during recovery. The sensitivity of chest CT was 97% in patients who ultimately had positive RT-PCR results. However, in this setting, 75% of patients with negative RT-PCR results also had positive chest CT findings. Of these patients, 48% were considered highly likely cases, while 33% were considered probable cases.[758]
**Diagnosis**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>Rapid antigen test</td>
<td>Positive for SARS-CoV-2 virus antigen</td>
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</table>

- Relies on direct detection of SARS-CoV-2 viral proteins in upper respiratory specimens or saliva using a lateral flow immunoassay. Results are usually available in less than 30 minutes. While antigen tests are substantially less sensitive than RT-PCR, particularly in asymptomatic people, they offer the possibility of rapid, inexpensive, and early detection of the most infectious cases in appropriate settings.[619]
- International guidelines on the use of rapid antigen tests vary. Consult your local guidance.
- The World Health Organization recommends antigen testing in symptomatic people who meet the case definition in the first 5 to 7 days of symptom onset, and to test asymptomatic people at high risk of infection, including contacts and health workers, particularly in settings where molecular testing capacity is limited. Tests should meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared with an RT-PCR reference assay. Results are most reliable in areas where there is ongoing community transmission.[619] Self-testing should be offered in addition to professionally administered testing services. It should always be voluntary and never mandatory or coercive.[620]
- In the UK, rapid antigen tests are recommended in certain situations, including: before visiting people who are at higher risk of severe disease; for contacts of a confirmed case who do not have to self-isolate; and for people who will be in high-risk situations on a

Transverse CT scans from a 32-year-old man, showing ground-glass opacity and consolidation of lower lobe of right lung near the pleura on day 1 after symptom onset (top panel), and bilateral ground-glass opacity and consolidation on day 7 after symptom onset.

Xu XW et al. BMJ. 2020;368:m606
<table>
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<tr>
<th>Test</th>
<th>Result</th>
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<tr>
<td>particular day (e.g., in crowded and enclosed spaces, or if there is limited fresh air).[621]</td>
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<tr>
<td>• In the US, the Infectious Diseases Society of America recommends antigen testing in some individuals only when molecular testing is not readily available or is logistically infeasible, noting that the overall quality of available evidence supporting its use was graded as very low to moderate.[622] The Centers for Disease Control and Prevention recommends antigen tests may be used in congregate and community settings; however, confirmatory molecular testing may be needed.[623] The US Food and Drug Administration has warned that false-positive results can occur with antigen tests, including when users do not follow the instructions for use, and that the number of false-positive tests increases as disease prevalence decreases.[624] The agency has also recommended not using certain tests due to performance issues.[759]</td>
<td></td>
</tr>
<tr>
<td>• A Cochrane review found that rapid antigen tests vary in sensitivity. Sensitivity was higher in the first week after symptom onset in symptomatic people (78.3%), compared with the second week of symptoms (51%). Sensitivity was higher in those with RT-PCR cycle threshold values ≤25 (94.5%), compared with those with cycle threshold values &gt;25 (40.7%). Sensitivity was higher in symptomatic people (72%), compared with asymptomatic people (58.1%). Sensitivity also varied between brands of tests. Positive predictive values suggest that confirmatory testing of those with positive results may be considered in low prevalence settings. Evidence for testing in asymptomatic cohorts was limited, and no studies assessed the accuracy of repeated lateral flow testing or self-testing.[625]</td>
<td></td>
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<tr>
<td>• Rapid antigen testing appears to be a reliable diagnostic tool to quickly detect people with a high viral load and in the first week of symptom onset, and can help to detect and isolate potential superspreaders before RT-PCR results are available. However, testing is unsuccessful in detecting people with lower viral load and asymptomatic patients.[629] [630]</td>
<td></td>
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<tr>
<td>• Rapid, lateral flow antigen tests for home use are available over-the-counter in some countries.[760]</td>
<td></td>
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<tr>
<td>• Laboratory-based (nonrapid) antigen tests are also available in some countries. [760]</td>
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<tr>
<td>• [BMJ: interpreting a lateral flow SARS-CoV-2 antigen test] (<a href="https://www.bmj.com/content/373/bmj.n1411">https://www.bmj.com/content/373/bmj.n1411</a>)</td>
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</table>

**serology**

- Important: a positive test for spike protein IgM or IgG could indicate either prior infection or prior vaccination with a COVID-19 vaccine. To evaluate for evidence of prior infection in an individual who has received a vaccine, a test that specifically evaluates IgM or IgG to the nucleocapsid protein should be used. A positive nucleocapsid protein-based assay indicates prior infection. Antibody testing is not currently recommended to assess immunity following vaccination.[338] [339] [340] [341]  
- Cannot be used as a standalone diagnostic for acute infections; however, may be useful in various settings (e.g, negative molecular testing, diagnosing patients with late presentation or prolonged symptoms, serosurveillance studies).[539] [613]  
- [BMJ practice pointer: testing for SARS-CoV-2 antibodies] (https://www.bmj.com/content/370/bmj.m3325)  
- The World Health Organization (WHO) recommends collecting a paired serum sample, one specimen in the acute phase and one positive for SARS-CoV-2 virus antibodies; seroconversion or a rise in antibody titers in paired sera
<table>
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<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>in the convalescent phase 2 to 4 weeks later, in patients where infection is strongly suspected and the RT-PCR result is negative. Seroconversion or a rise in antibody titers in paired sera help to confirm whether the infection is recent and/or acute. If the initial sample tests positive, this could be due to a past infection that is not related to the current illness. Seroconversion may be faster and more robust in patients with severe disease compared with those with mild disease or asymptomatic infection.</td>
<td><strong>[539]</strong></td>
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<tr>
<td>• The Centers for Disease Control and Prevention recommends serologic testing as a method to support the diagnosis of illness or complications in the following situations: a positive antibody test at least 7 days following acute illness onset in people with a previous negative antibody test (i.e., seroconversion) and who did not receive a positive viral test may indicate SARS-CoV-2 infection between the dates of the negative and positive antibody tests; a positive antibody test can help support a diagnosis when patients present with complications of COVID-19 illness, such as multisystem inflammatory syndrome and other post-acute sequelae of COVID-19.</td>
<td><strong>[614]</strong></td>
</tr>
<tr>
<td>• The Infectious Diseases Society of America recommends serologic testing in the following circumstances: evaluation of patients with a high clinical suspicion for infection when molecular diagnostic testing is negative and at least 2 weeks have passed since symptom onset; evaluation of pediatric inflammatory multisystem syndrome in children; and serosurveillance studies.</td>
<td><strong>[615]</strong></td>
</tr>
<tr>
<td>• Antibody responses to SARS-CoV-2 typically occur during the first 1 to 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.</td>
<td><strong>[616]</strong> [617]</td>
</tr>
<tr>
<td>• The estimated sensitivity of antibody tests ranged from 18.4% to 96.1% (the lowest reported sensitivity was from a point-of-care test, although a sensitivity &lt;50% was reported for one laboratory test), and specificity ranged from 88.9% to 100%. Estimates of diagnostic accuracy need to be interpreted with caution in the absence of a definitive reference standard to diagnose or rule out COVID-19.</td>
<td><strong>[599]</strong></td>
</tr>
<tr>
<td>• Limitations of testing: serologic testing cannot be used to determine acute infection; results do not indicate the presence or absence of current or previous infection with certainty; reliable diagnosis is often only possible in the recovery phase when opportunities for management or interruption of transmission have passed; cross-reactivity with other coronaviruses, which can result in false-positive results.</td>
<td><strong>[539]</strong> [614]</td>
</tr>
<tr>
<td>• While rapid antibody detection kits have been approved for the qualitative detection of SARS-CoV-2 IgG/IgM antibodies in serum, plasma, or whole blood, the WHO does not recommend the use of these tests outside of research settings as they have not been validated as yet.</td>
<td><strong>[631]</strong></td>
</tr>
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</table>
## Emerging tests

<table>
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<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td><strong>lung ultrasound</strong></td>
<td>B-lines; pleural abnormalities</td>
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</table>
| • Lung ultrasound is used as a diagnostic tool in some centers as an alternative to chest x-ray and chest CT. Although there is only very low-certainty evidence supporting its diagnostic accuracy, it might be helpful as a supplemental or alternate imaging modality.\[636\]  
  • Ultrasound is sensitive but not specific for the diagnosis of COVID-19. Pooled results found that lung ultrasound correctly diagnosed COVID-19 in 86.4% of people with the disease. However, it incorrectly diagnosed COVID-19 in 45% of people who did not have the disease. Therefore, ultrasound may have more utility for excluding COVID-19 than for differentiating it from other causes of respiratory illness.\[635\]  
  It may also be useful for triage in the emergency department.\[761\]  
  • B-lines (confluent or separated and usually at least 3) and pleural abnormalities, with a bilateral distribution, are the most frequent findings in COVID-19. Other findings include consolidations, pleural effusion, air bronchogram, and pneumothorax.\[652\] While these findings are not specific for COVID-19, they increase the likelihood of disease in the context of a characteristic clinical presentation.  
  • Has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, easier sterilization process, absence of ionizing radiation exposure, and repeatability during follow-up. It may also be more readily available in resource-limited settings. However, it also has some limitations (e.g., it is unable to discern chronicity of a lesion) and other imaging modalities may be required. May be used in pregnant women and children.\[653\] [654] [655]  
  • Possible roles include: reducing nosocomial transmission; monitoring progress of patients; and a possible role in subpopulations who are vulnerable but are not suitable for CT (e.g., pregnant women)\[656\]  
  Lung ultrasound score may play a role in prognosis.\[657\]  
| **reverse transcription loop-mediated isothermal amplification (RT-LAMP)** | positive for SARS-CoV-2 viral RNA |
| • A similar process to RT-PCR, but uses constant temperatures and produces more viral DNA compared with RT-PCR. While simple and quick, it is a newer technology and there is less evidence for its use. Assays for SARS-CoV-2 have been developed and are being evaluated.\[658\] [659] [660]  
  • RT-LAMP appears to be a reliable assay, comparable to RT-PCR, particularly with medium to high viral loads (i.e., cycle threshold <35), especially in resource-limited settings.\[661\] A sensitivity of 95.5% and specificity of 99.5% has been reported.\[662\]  
  • An at-home test kit that provides rapid results within 30 minutes has been approved in the US under an emergency-use authorization for self-testing at home that provides rapid results.\[762\] |
| **CRISPR-based diagnostics**              | positive for SARS-CoV-2 viral RNA |
| • Clustered regularly interspaced short palindromic repeats (CRISPR)-based diagnostic methods have been developed for detecting SARS-CoV-2 viral RNA. These simple, high-throughput molecular tests have the advantage of providing results in less than 1 hour, can be used |
### Diagnosis

<table>
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<tr>
<th>Test</th>
<th>Result</th>
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</table>
| with various specimens, and have high specificity/sensitivity (similar to RT-PCR)\(^{[663]}\) \(^{[664]}\) \(^{[665]}\)  
- Various CRISPR-based tests have been granted emergency-use authorization by the US Food and Drug Administration. |         |
| breathalyzers             | positive |
| - Breath analysis has been shown to have potential in diagnosing COVID-19 by analyzing volatile organic compounds in exhaled breath\(^{[666]}\)  
- The US Food and Drug Administration has issued an emergency-use authorization for the first COVID-19 diagnostic test that detects chemical compounds in breath samples associated with SARS-CoV-2 infection. The test has been shown to have 91.2% sensitivity and 99.3% specificity in one company-sponsored study of 2409 participants, including those with and without symptoms\(^{[667]}\)  
However, the test currently has many limitations (e.g., size of the device, number of samples that can be processed, lack of evidence for this method of diagnosis, other diseases or food/drinks that can affect result, test result is presumptive and still requires confirmation), and more research is required. |         |
| calprotectin              | elevated |
| - Calprotectin is an emerging biomarker of interest. Calprotectin levels often increase following infection or trauma, and in inflammatory disease. Serum/fecal calprotectin levels have been demonstrated to be significantly elevated in COVID-19 patients with severe disease, and it may have prognostic significance\(^{[668]}\) \(^{[669]}\) |         |
## Differentials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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| Community-acquired pneumonia| - Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
- Differentiating COVID-19 from community-acquired bacterial pneumonia is not usually possible from signs and symptoms. However, patients with bacterial pneumonia are more likely to have rapid development of symptoms and purulent sputum. They are less likely to have myalgia, anosmia, or pleuritic pain.[763] | - Blood or sputum culture or molecular testing: positive for causative organism.  
- RT-PCR: negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA (coinfections are possible).  
- CT chest: centrilobular nodules, mucoid impactions.[764] |
| Influenza infection         | - Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
- Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.  
- Incubation period is shorter.[765] Symptoms typically peak during the first 3 to 7 days of illness with influenza, compared with week 2 or 3 of illness with COVID-19.[766]  
- More common in children.[766] Children with COVID-19 tend to be older, and are more likely to have comorbidities, fever, gastrointestinal symptoms, headache, and chest pain compared with those with influenza.[767]  
- Fever is less common. Rhinorrhea, sore throat, myalgia, headache, and dyspnea are more common. | - Only testing can distinguish between influenza infection and COVID-19 and identify coinfection.  
- RT-PCR: positive for influenza A or B viral RNA; negative for SARS-CoV-2 viral RNA (coinfections are possible).  
- Chest x-ray: less likely to be abnormal.[765]  
- CT chest: there is emerging evidence that CT can be used for differentiating between influenza and COVID-19. COVID-19 patients are more likely to have rounded or linear opacities, crazy-paving sign, vascular enlargement, and interlobular septal thickening, but less likely to have nodules, tree-in-bud sign, bronchiectasis, and pleural effusion.[772] [773]  
- Inflammatory markers and coagulation screen: there is emerging evidence that inflammatory markers (lactate dehydrogenase, erythrocyte sedimentation rate, C-reactive protein) and
<table>
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<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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</table>
| Common cold                       | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
  • Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. However, fever is less common, and headache, rhinorrhea, myalgia, and sore throat are more common. Patients may have a greater number of general symptoms.[768] | • RT-PCR: positive for causative organism; negative for SARS-CoV-2 viral RNA (coinfections are possible). |
| Other viral or bacterial respiratory infections | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
  • Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.  
  • Adenovirus and Mycoplasma should be considered in clusters of pneumonia patients, especially in closed settings such as military camps and schools. | • Blood or sputum culture of molecular testing: positive for causative organism.  
  • RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible). |
| Aspiration pneumonia              | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case | • RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible).  
  • CT chest: difficult to distinguish on CT; however, anterior lung involvement |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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| **Pneumocystis jirovecii pneumonia** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
• Differentiating COVID-19 from pneumocystis jirovecii pneumonia is not usually possible from signs and symptoms.  
• Patients are usually immunocompromised (e.g., HIV positive) and duration of symptoms may be longer. | • Sputum culture: positive for *Pneumocystis*.  
• RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible).  
• CT chest: ground-glass opacity is usually more diffusely distributed with a tendency to spare the subpleural regions.[764] |
| **Middle East respiratory syndrome (MERS)** | • Travel history to the Middle East or contact with a confirmed case of MERS.  
• Differentiating COVID-19 from MERS is not possible from signs and symptoms.  
• Initial data suggest that the clinical course of COVID-19 is less severe and the case fatality rate is lower compared with MERS. | • Reverse-transcriptase polymerase chain reaction (RT-PCR): positive for MERS-CoV viral RNA. |
| **Avian influenza A (H7N9) virus infection** | • May be difficult to differentiate based on epidemiologic history as avian influenza H7N9 is endemic in China.  
• Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area when avian influenza is endemic. | • RT-PCR: positive for H7-specific viral RNA. |
| **Avian influenza A (H5N1) virus infection** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset. | • RT-PCR: positive for H5N1 viral RNA. |
### Condition | Differentiating signs / symptoms | Differentiating tests
--- | --- | ---
**Coronavirus disease 2019 (COVID-19)**

- Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area when avian influenza is endemic.

**Pulmonary tuberculosis**

- Consider diagnosis in endemic areas, especially in patients who are immunocompromised.
- History of symptoms is usually longer.
- Presence of night sweats and weight loss may help to differentiate.

- Chest x-ray: fibronodular opacities in upper lobes with or without cavitation; atypical pattern includes opacities in middle or lower lobes, or hilar or paratracheal lymphadenopathy, and/or pleural effusion.
- Sputum acid-fast bacilli smear and sputum culture: positive.
- Molecular testing: positive for *Mycobacterium tuberculosis*.

**Febrile neutropenia**

- Suspect neutropenic sepsis in patients with a history of recent systemic anticancer treatment who present with fever (with or without respiratory symptoms) as this can be rapid and life-threatening.[776]
- Symptoms of COVID-19 and neutropenic sepsis may be difficult to differentiate at initial presentation. Patients with febrile neutropenia are at increased risk of COVID-19.[777]

- CBC: neutropenia.
- RT-PCR: negative for SARS-CoV-2 viral RNA.

**Other**

- COVID-19 should be considered a differential diagnosis for many conditions. The differential is very broad and includes many common respiratory, infectious, cardiovascular, oncologic, and gastrointestinal diseases.[778]

- RT-PCR: negative for SARS-CoV-2 viral RNA.
- Other differentiating tests depend on the suspected diagnosis.

### Criteria

**World Health Organization: COVID-19 disease severity[87]**

Mild illness
Coronavirus disease 2019 (COVID-19)

Diagnosis

• Symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia.
• Common symptoms include fever, cough, fatigue, anorexia, dyspnea, and myalgia. Other nonspecific symptoms include sore throat, nasal congestion, headache, diarrhea, nausea/vomiting, and loss of smell/taste. Additional neurologic manifestations reported include dizziness, agitation, weakness, seizures, or findings suggestive of stroke. Children may not report fever or cough as frequently as adults.
• Older people and immunosuppressed people may present with atypical symptoms (e.g., fatigue, reduced alertness, reduced mobility, diarrhea, loss of appetite, delirium, absence of fever).
• Symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events (e.g., dyspnea, fever, gastrointestinal symptoms, fatigue) or other diseases (e.g., malaria) may overlap with COVID-19 symptoms.

Moderate disease

• Adolescent or adult: clinical signs of pneumonia (i.e., fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including blood oxygen saturation levels (SpO₂) ≥90% on room air.
• Children: clinical signs of nonsevere pneumonia (i.e., cough or difficulty breathing plus fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing is defined as:
  - <2 months of age: ≥60 breaths/minute
  - 2-11 months of age: ≥50 breaths/minute
  - 1-5 years of age: ≥40 breaths/minute.
• While the diagnosis can be made on clinical grounds, chest imaging may assist in diagnosis and identify or exclude pulmonary complications.

Severe disease

• Adolescent or adult: clinical signs of pneumonia (i.e., fever, cough, dyspnea, fast breathing) plus one of the following:
  - Respiratory rate >30 breaths/minute
  - Severe respiratory distress
  - SpO₂ <90% on room air.
• Children: clinical signs of pneumonia (i.e., cough or difficulty in breathing) plus at least one of the following:
  - Central cyanosis or SpO₂ <90%
  - Severe respiratory distress (e.g., fast breathing, grunting, very severe chest indrawing)
  - General danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions
  - Fast breathing (<2 months: ≥60 breaths per minute; 2-11 months: ≥50 breaths per minute; 1-5 years: ≥40 breaths per minute).
• While the diagnosis can be made on clinical grounds, chest imaging may assist in diagnosis and identify or exclude pulmonary complications.

Critical disease
• Presence of acute respiratory distress syndrome (ARDS), sepsis, septic shock, acute thrombosis, or multisystem inflammatory syndrome in children.

### National Institutes of Health: clinical classification of COVID-19[19]

#### Asymptomatic or presymptomatic infection

• People who test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using a virologic test but have no symptoms consistent with COVID-19.

#### Mild illness

• People who have any of various signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) without shortness of breath, dyspnea, or abnormal chest imaging.

#### Moderate illness

• People who have evidence of lower respiratory disease by clinical assessment or imaging and an oxygen saturation (SpO₂) ≥94% on room air at sea level.

#### Severe illness

• People who have respiratory frequency >30 breaths per minute, SpO₂ <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) <300 mmHg, or lung infiltrates >50%.

#### Critical illness

• People who have respiratory failure, septic shock, and/or multiple organ dysfunction.

### Persistent symptoms or organ dysfunction after acute COVID-19

• People who experience persistent symptoms and/or organ dysfunction after acute disease. Also known as post-acute COVID-19 syndrome or long COVID. See the Complications section for more information.

### Case definitions

Various case definitions are available:

Screening

Management of contacts

Definition

- The World Health Organization defines a contact as a person who has experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:[779]
  - Face-to-face contact with a probable or confirmed case within 3 feet (1 meter) and for more than 15 minutes
  - Direct physical contact with a probable or confirmed case
  - Direct care for a patient with probable or confirmed COVID-19 without using recommended personal protective equipment
  - Other situations as indicated by local risk assessments.
- The Centers for Disease Control and Prevention (CDC) defines a close contact as someone who has been within 6 feet (2 meters) of an infected person for at least 15 minutes over a 24-hour period, beginning 2 days before symptom onset (or 2 days before testing in asymptomatic patients).[125]
- Consult local guidance as definitions of a contact may vary depending on local public health advice.

Quarantine periods

- The World Health Organization recommends that asymptomatic contacts of confirmed or probable cases, including healthcare workers, be quarantined in a designated facility or in a separate room in the household for 14 days from the last contact with the case. Any person in quarantine who develops symptoms should be treated and managed as a suspected case and tested according to national testing strategies and guidelines. Laboratory testing is not a requirement for leaving quarantine after 14 days for contacts who do not develop symptoms.[779] Testing can be used as a measure to shorten quarantine (e.g., to 7 days) if the contact shows no symptoms and presents a negative test, in the context of the Omicron variant. Where testing to shorten quarantine is not possible, quarantine may be ended after 10 days without testing if the contact presents no symptoms.[780] Testing can be used as a measure to shorten quarantine (e.g., to 7 days) if the contact shows no symptoms and presents a negative test, in the context of the Omicron variant. Where testing to shorten quarantine is not possible, quarantine may be ended after 10 days without testing if the contact presents no symptoms.[780]
- In the UK, contacts are no longer required to self-isolate.[781]
- In the US, the CDC recommends that contacts who are up-to-date with vaccinations do not need to quarantine unless they develop symptoms. However, they should get tested at least 5 days after their exposure even if they don’t develop symptoms (except people with confirmed COVID-19 within the past 90 days), and take precautions until day 10 (e.g., wear a mask around others, take precautions if traveling, avoid being around people who are at high risk). Contacts who are not up-to-date with their vaccinations are required to quarantine for at least 5 days, get tested at least 5 days after their exposure even if they don’t develop symptoms, and take the same precautions until day 10.[782]
- Consult local guidance for recommended quarantine locations and timeframes as recommendations vary depending on local public health advice.

Screening of asymptomatic populations

The World Health Organization does not currently recommend widespread screening of asymptomatic individuals due to the significant costs associated with it and the lack of data on its operational effectiveness. Testing of asymptomatic individuals is currently recommended only for specific groups including contacts of confirmed or probable cases and frequently exposed groups such as healthcare workers and long-term care facility workers.[581]
Drive-through screening centers

Drive-through screening centers have been set up in some countries for safer and more efficient screening. The testee does not leave their car throughout the entire process, which includes registration and questionnaire, exam, specimen collection, and instructions on what to do after. This method has the advantage of increased testing capacity and prevention of cross-infection between testees in the waiting space.[783]

Temperature screening

There is little scientific evidence to support temperature screening with thermal cameras or temperature screening products (e.g., noncontact infrared thermometers) as a reliable method for the detection of COVID-19 or any other febrile illness, especially if used as the main method of testing.[784] [785] [786]
Approach

Management predominantly depends on disease severity, and focuses on the following principles: isolation at a suitable location; infection prevention and control measures; symptom management; prevention of disease progression; optimized supportive care; and organ support in severe or critical illness.

Best Practice has published a separate topic on the Management of coexisting conditions in the context of COVID-19.

Key recommendations

- Consider whether the patient can be managed at home. Generally, patients with asymptomatic or mild disease can be managed at home or in a community facility.[87]
- Consider monoclonal antibody treatment in patients with nonsevere disease who are at highest risk of hospitalization. Moderate-quality evidence suggests that monoclonal antibodies may reduce the risk of hospitalization and duration of symptoms. They may also be considered in seronegative patients with severe disease. Low- to moderate-quality evidence suggests that they may reduce the need for mechanical ventilation and mortality.[21] [795] [796]
- Admit patients with moderate or severe disease to an appropriate healthcare facility. Assess adults for frailty on admission. Patients with critical disease require intensive care; involve the critical care team in discussions about admission to critical care when necessary. Monitor patients closely for signs of disease progression.[87] [20]
- Provide symptom relief as necessary. This may include treatments for fever, cough, breathlessness, anxiety, delirium, or agitation.[87] [20]
- Start supportive care according to the clinical presentation. This might include oxygen therapy, intravenous fluids, venous thromboembolism prophylaxis, high-flow nasal oxygen (HFNO), noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. Sepsis and septic shock should be managed according to local protocols.[87]
- Consider empiric antibiotics if there is clinical suspicion of a secondary bacterial infection. Antibiotics may be required in patients with moderate, severe, or critical disease. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria. Base the regimen on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.[87] [20]
- Consider systemic corticosteroid therapy for 7 to 10 days in patients with severe or critical disease. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe and critical disease, and probably reduce the need for invasive ventilation.[19] [21]
- Consider remdesivir in patients with severe or critical disease. There are conflicting recommendations across international guidelines about the use of remdesivir. While UK and US guidelines recommend considering remdesivir in certain patients, the World Health Organization recommends against its use.[19] [20] [21] Some guidelines also recommend remdesivir in patients with mild to moderate disease who are at high risk of clinical progression.[19]
- Consider an interleukin-6 inhibitor (tocilizumab or sarilumab) or a Janus kinase inhibitor (baricitinib) in patients with severe or critical disease. High-certainty evidence suggests that interleukin-6 inhibitors reduce mortality and the need for mechanical ventilation. Moderate-certainty evidence suggests that Janus kinase inhibitors reduce mortality and duration of mechanical ventilation.[21] [795] [796]
• Assess whether the patient requires any rehabilitation or follow-up after discharge. Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[87]
• For full details and guidance see information below.

Infection prevention and control
Implement local infection prevention and control procedures when managing patients. For patients in home isolation, advise patients and household members to follow appropriate infection prevention and control measures:


Guidance on when to stop isolation varies widely across locations.

• Isolation periods may depend on various factors including vaccination status, circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, and patient factors (e.g., immunocompetent/immunocompromised, asymptomatic/symptomatic, disease severity).
• The World Health Organization recommends discontinuing transmission-based precautions (including isolation) and releasing patients from the care pathway 10 days after positive test (asymptomatic patients), or 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms (symptomatic patients).[87]
• However, some countries now recommend isolation periods as short as 5 days to 7 days.[797]
• Consult your local public health guidance for more information.

Mild COVID-19
Patients with suspected or confirmed mild disease (i.e., symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia) and asymptomatic patients should be isolated to contain virus transmission.[87] Approximately 80% of patients have mild illness that does not warrant medical intervention or hospitalization.[19]

Location of care

• Manage patients in a healthcare facility, a community facility, or at home. Home isolation can be considered in most patients, with telemedicine or remote visits as appropriate.[87][19]

• There is some evidence to suggest that implementation of an early home treatment algorithm reduced the risk of hospitalization and related treatment costs in a small cohort of patients.[798]
• This decision requires careful clinical judgment and should be informed by an assessment of the patient’s home environment to ensure that: infection prevention and control measures and other requirements can be met (e.g., basic hygiene, adequate ventilation); the caregiver is able to provide
care and recognize when the patient may be deteriorating; the caregiver has adequate support (e.g., food, supplies, psychological support); the support of a trained health worker is available in the community.[799]

Symptom management

- Fever and pain: acetaminophen or ibuprofen are recommended.[87] [20] Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms.
- Cough: advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough.[20]
  - A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[800]
- Olfactory dysfunction: consider treatment (e.g., olfactory training) if olfactory dysfunction persists beyond 2 weeks. Often it improves spontaneously and does not require specific treatment. There is no evidence to support the use of treatments in patients with COVID-19.[801]
  - A Cochrane review found there is very limited evidence regarding the efficacy of different interventions at preventing persistent olfactory dysfunction following infection. The only evidence available is for intranasal corticosteroids, and this is of very low certainty, so no conclusions could be drawn.[802]

Supportive care

- Advise patients about adequate nutrition and appropriate rehydration. Advise patients to drink fluids regularly to avoid dehydration. Fluid intake needs can be higher than usual because of fever. However, too much fluid can worsen oxygenation.[87] [20]
- Advise patients to improve air circulation by opening a window or door.[20]
- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[87]
- Most children with mild disease can be managed with supportive care alone and will not require any specific therapy.[19]

Monoclonal antibodies

- Monoclonal antibodies are authorized for use in some countries; however, availability and indications vary between countries. Consult your local guidance for more information.
  - Options may include casirivimab/imdevimab, sotrovimab, bamlanivimab/etesevimab, bebtelovimab, and regdanvimab, depending on your location.
  - The antibodies used in these combinations bind to nonoverlapping epitopes of the receptor-binding domain of the spike protein to block virus entry into host cells.
- Choice of monoclonal antibody depends on availability, as well as clinical and contextual factors including emerging information about efficacy with different variants.[19] [20] [21]
  - Preclinical evidence has emerged suggesting that casirivimab/imdevimab and bamlanivimab/etesevimab lack neutralization activity against the Omicron variant in vitro. Sotrovimab and
bebtelovimab appear to retain activity against Omicron; however, sotrovimab is not active against the Omicron BA.2 subvariant.  

- Logistical or supply constraints may make patient triage for monoclonal antibody treatment necessary. Therapy should be prioritized for patients who are at the highest risk of progressing to severe disease.  

- The World Health Organization recommends sotrovimab or casirivimab/imdevimab for patients with nonsevere disease who are at highest risk of hospitalization.[21] [795] [796]  

- Casirivimab/imdevimab should only be used where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e., excluding Omicron).  
- Monoclonal antibodies probably reduce the risk of hospitalization and duration of symptoms in patients with nonsevere disease, based on moderate-certainty evidence.  
- While monoclonal antibodies achieve a substantial reduction in the relative risk of hospitalization, the absolute benefit will be trivial or unimportant in absolute terms for all but those who are at highest risk of disease (e.g., unvaccinated, older people, immunodeficiencies, and/or chronic disease).  
- Treatment is in addition to the current standard of care.  
- The applicability of this recommendation to children is currently uncertain.  

- In the UK, the National Institute for Health and Care Excellence recommends offering a neutralizing monoclonal antibody to patients ≥12 years of age who are not in hospital and are thought to be at high risk of progression to severe disease.[20]  

- Consult local guidance for monoclonal antibodies with current UK access.  

- In the US, the National Institutes of Health guidelines panel recommends bebtelovimab for the treatment of nonhospitalized patients with mild to moderate disease who are at high risk of clinical progression. However, it is only recommended when preferred therapies (i.e., antivirals) are not available, feasible to use, or clinically appropriate as it has not been evaluated in patients at high risk of progression in placebo-controlled trials.[19]  

- Treatment should be started as soon as possible and within 10 days of symptom onset.  
- Use may be considered in patients with mild to moderate disease who are hospitalized for a reason other than COVID-19, provided that they otherwise meet the criteria for outpatient treatment.  
- The panel currently recommends against the use of casirivimab/imdevimab, bamlanivimab/etesevimab, and sotrovimab because Omicron is the dominant variant in the US, and these monoclonal antibodies are predicted to have markedly reduced susceptibility to Omicron and its subvariants. These monoclonal antibodies are not currently authorized for use in the US.[803] [804]  
- The Infectious Diseases Society of America supports the use of monoclonal antibodies in ambulatory patients with mild to moderate disease who are at high risk for progression to severe disease, although it only recommends bebtelovimab in the context of a clinical trial.[510]  

- Monoclonal antibodies are administered by intravenous infusion.  

- Casirivimab/imdevimab is also available in a subcutaneous formulation, but intravenous administration is recommended. However, if intravenous infusions are not feasible or would
cause a delay in treatment, subcutaneous administration may be considered.[19] Evidence for subcutaneous administration is emerging.[805]

- Outpatient administration in specialized clinics is required, which may limit the feasibility of these treatments.[21]

- Evidence for the use of monoclonal antibodies in nonhospitalized patients is uncertain.

- A Cochrane review found that the evidence is insufficient to draw meaningful conclusions about any specific monoclonal antibody, and the disease stage in which it should be used. Information on outcomes in nonhospitalized patients such as mortality, quality of life, and serious adverse events is either inconclusive or entirely lacking, although casirivimab/imdevimab, sotrovimab, bamlanivimab (alone or in combination with etesevimab), and regdanvimag may reduce the occurrence of hospital admission or death (low-certainty evidence).[806]

Antivirals

- Antiviral agents are recommended in some countries for patients with mild to moderate disease who are at high risk of clinical progression.

- The World Health Organization conditionally recommends the intravenous antiviral remdesivir for patients with nonsevere disease who are at highest risk of hospitalization.[21] [795] [796]

  - Remdesivir should be administered as soon as possible after onset of symptoms, ideally within 7 days. The treatment course for this indication is 3 days.
  
  - It is not recommended in children <12 years of age (or weighing <40 kg).
  
  - Remdesivir probably reduces hospital admission (moderate-certainty evidence), and may have little or no impact on mortality (low-certainty evidence). The effect on mechanical ventilation and time to symptom resolution is very uncertain. The balance between benefits and potential harms favors treatment, but only in the highest risk group.

  - In the UK, the National Institute for Health and Care Excellence recommends remdesivir for patients ≥12 years of age (weighing ≥40 kg) who do not need supplemental oxygen, and are within 7 days of symptom onset, and are thought to be at high risk of progression to severe disease (based on low-certainty evidence).[20]

  - In the US, the National Institutes of Health guidelines panel recommends remdesivir to treat nonhospitalized patients with mild to moderate disease who are at high risk of clinical progression.[19]

    - If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the healthcare provider’s discretion.

    - The Infectious Diseases Society of America supports the use of remdesivir in ambulatory patients with mild to moderate disease who are at high risk for progression to severe disease.[510]

    - Remdesivir is approved in pediatric patients ≥28 days of age (weighing at least 7 lbs [3 kg]) in the US.[807]

    - Evidence for this indication is emerging.

    - A randomized, double-blind, placebo-controlled trial of 562 patients found that a 3-day course of remdesivir resulted in an 87% lower risk of hospitalization or death among
nonhospitalized patients who were at high risk for disease progression compared with placebo. The most common coexisting conditions were diabetes, obesity, and hypertension.[808]

- Logistical or supply constraints may make patient triage for antiviral treatment necessary. Therapy should be prioritized for patients who are at the highest risk of progressing to severe disease.
  - Logistical constraints may make it difficult to administer the drug in some outpatient settings as it requires administration via intravenous infusion.
  - Oral antiviral agents (e.g., molnupiravir, nirmatrelvir/ritonavir) are also available and may be recommended for patients with mild to moderate disease who are at high risk for progression to severe disease. See the Emerging section for more information.

Monitor

- Closely monitor patients with risk factors for severe illness, and counsel patients about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain).[87] [19]
  - Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalized. Patient education and appropriate follow-up are required.[87]

Corticosteroids

- Guidelines do not recommend systemic corticosteroids in patients with non-severe disease, unless there is another medical indication to do so, as they may increase the risk of mortality in these patients.[19] [20] [21]

Antithrombotic therapy

- Guidelines recommend against the use of anticoagulants and antiplatelet therapy for the prevention of venous thromboembolism or arterial thrombosis in nonhospitalized patients without evidence of venous thromboembolism, unless the patient has other indications for therapy or is participating in a clinical trial.[19]

Moderate COVID-19

Patients with suspected or confirmed moderate disease (i.e., clinical signs of pneumonia but no signs of severe pneumonia) should be isolated to contain virus transmission.[87]

Location of care

- Manage patients in a healthcare facility, in a community facility, or at home. Home isolation, with telemedicine or remote visits as appropriate, can be considered in low-risk patients (i.e., patients who are not at high risk of deterioration). Manage patients at high risk of deterioration in a healthcare facility.[87] [19]

Symptom management and supportive care

- Manage symptoms and provide supportive care as appropriate (see Mild COVID-19 above).
  - Most children with moderate disease can be managed with supportive care alone and will not require any specific therapy.[19]
Antibiotics

- Consider empiric antibiotics only if there is clinical suspicion of secondary bacterial infection. Start treatment as soon as possible, and refer to local guidelines for choice of regimen.[87] [19] [20] Do not offer an antibiotic for preventing secondary bacterial pneumonia.[20]
- Antibiotics may also be considered in older people (particularly those in long-term care facilities) and children <5 years of age to provide empiric antibiotic treatment for possible pneumonia.[87]
- Advise patients to seek medical help without delay if their symptoms do not improve, or worsen rapidly or significantly. Reconsider whether the person has signs and symptoms of more severe disease on reassessment, and whether to refer them to hospital, other acute community support services, or palliative care services.[20]

Monoclonal antibodies and antivirals

- Consider the use of a monoclonal antibody and/or an antiviral agent in nonhospitalized patients with mild to moderate disease who are at high risk of clinical progression (see Mild COVID-19 above).

Monitor

- Closely monitor patients for signs or symptoms of disease progression.
- If the patient is being managed at home, counsel them about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain). Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalized. Patient education and appropriate follow-up are required.[87]
- If the patient is being managed in hospital, monitor patients closely for signs of clinical deterioration using medical early warning scores (e.g., National Early Warning Score 2 [NEWS2]), and respond immediately with appropriate supportive care interventions.[87]

  - A systematic review and meta-analysis found that the NEWS2 score had moderate sensitivity and specificity in predicting the deterioration of patients with COVID-19. The score showed good discrimination in predicting the combined outcome of the need for intensive respiratory support, admission to the intensive care unit, or in-hospital mortality.[571]

Corticosteroids

- Guidelines do not recommend systemic corticosteroids in patients with nonsevere disease, unless there is another medical indication to do so, as they may increase the risk of mortality in these patients.[19] [20] [21] However, the US the National Institutes of Health guideline panel recommends oral dexamethasone in patients who are discharged from the emergency department despite new or increased need for supplemental oxygen (for the duration of supplemental oxygen and not to exceed 10 days), when hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured.[19]

Antithrombotic therapy

- Guidelines recommend against the use of anticoagulants and antiplatelet therapy for the prevention of venous thromboembolism or arterial thrombosis in nonhospitalized patients without evidence of
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Management

venous thromboembolism, unless the patient has other indications for therapy or is participating in a clinical trial.[19]

Severe COVID-19

Patients with suspected or confirmed severe disease are at risk of rapid clinical deterioration.[87]

- Severe disease in adults is defined as having clinical signs of pneumonia plus at least one of the following:
  - Respiratory rate >30 breaths/minute
  - Severe respiratory distress
  - SpO₂ <90% on room air
- Severe disease in children is defined as having clinical signs of pneumonia plus at least one of the following:
  - Central cyanosis or SpO₂ <90%
  - Severe respiratory distress
  - General danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions
  - Fast breathing (<2 months: ≥60 breaths per minute; 2-11 months: ≥50 breaths per minute; 1-5 years: ≥40 breaths per minute).

The median time from onset of symptoms to hospital admission is around 7 days.[47] [675] Children are less likely to require hospitalization, but, if admitted, generally only require supportive care.[31] [809]

Location of care

- Manage patients in an appropriate healthcare facility under the guidance of a specialist team.[87]
- Use the Clinical Frailty Scale (CFS) to assess baseline health and inform discussions on treatment expectations when appropriate and within an individualized assessment of frailty. [Clinical Frailty Scale] (https://www.scfn.org.uk/clinical-frailty-scale) Do not use the CFS for younger people, or for people with stable long-term disabilities (e.g., cerebral palsy), learning disabilities, or autism. Make an individualized assessment of frailty in these people, using clinical assessment and alternative scoring methods.[20]

- Hospitalized frail patients are at higher risk of all-cause mortality compared with non-frail hospitalized patients, regardless of the frailty score/assessment tool used.[810]
- A meta-analysis found that an increase in CFS was associated with an increase in mortality (each 1-point increase in CFS was associated with a 12% increase in mortality).[811]
- Patients with a score between 4-9 had significantly increased mortality compared with those with a score of 1-3.[812]
- However, one systematic review and meta-analysis found that there was no difference in short-term mortality between frail and nonfrail patients.[813] Some studies suggest that a more nuanced understanding of frailty and outcomes is needed, and you should exercise caution in placing too much emphasis on the influence of frailty alone when discussing prognosis in older people.[814]

Oxygen
• Start supplemental oxygen therapy immediately in any patient with emergency signs (i.e., obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions), or any patient without emergency signs and SpO₂ <90%. [87] [19]

• There is no evidence of benefit for oxygen therapy in patients with COVID-19 in the absence of hypoxemia. [815]

• Target SpO₂ to ≥94% during resuscitation in adults and children with emergency signs who require emergency airway management and oxygen therapy. Once the patient is stable, a target SpO₂ >90% in children and nonpregnant adults, and ≥92% to 95% in pregnant women is recommended. Nasal prongs or a nasal cannula are preferred in young children. [87]

• Some guidelines recommend that SpO₂ should be maintained no higher than 96%. [816]

• Some centers may recommend different SpO₂ targets in order to support prioritization of oxygen flow for the most severely ill patients in hospital.

• Consider positioning techniques (e.g., high supported sitting), and airway clearance management to optimize oxygenation and assist with secretion clearance in adults. Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require supplemental oxygen. [87] [19]

• Awake prone positioning of nonintubated patients was associated with improvement in oxygen variables (PaO₂/FiO₂, PaO₂, and SpO₂), respiratory rate, rate of intubation, and mortality. However, evidence is limited. [817] [818] [819] [820] However, one small nonrandomized controlled trial found that prone positioning offered no clinical benefit among patients with hypoxemia who are not on mechanical ventilation, with evidence of worsening clinical outcomes at day 5. [821]

• Monitor patients closely for signs of progressive acute hypoxemic respiratory failure. Patients who continue to deteriorate despite standard oxygen therapy require advanced oxygen/ventilatory support. [87] [19]

Symptom management and supportive care

• Fluids and electrolytes: use cautious fluid management in adults and children without tissue hypoperfusion and fluid responsiveness as aggressive fluid resuscitation may worsen oxygenation. [87] Correct any electrolyte or metabolic abnormalities, such as hyperglycemia or metabolic acidosis, according to local protocols. [822]

• Fever and pain: acetaminophen or ibuprofen are recommended. [87] [20] Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms.

• Cough: advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough. Short-term use of a cough suppressant may be considered in select patients (e.g., if the cough is distressing to the patient) provided there are no contraindications. [20]

• A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity. [800]
Management

- Breathlessness: keep the room cool, and encourage relaxation, breathing techniques, and changing body positions. Identify and treat any reversible causes of breathlessness (e.g., pulmonary edema, pulmonary embolism, COPD, asthma).[20]
- Anxiety, delirium, and agitation: identify and treat any underlying or reversible causes (e.g., offer reassurance, treat hypoxia, correct metabolic or endocrine abnormalities, address coinfections, minimize use of drugs that may cause or worsen delirium, treat substance withdrawal, maintain normal sleep cycles, treat pain or breathlessness).[87] [20]
  - Low doses of haloperidol (or another suitable antipsychotic) can be considered for agitation.[87]
  - Nonpharmacologic interventions are the mainstay for the management of delirium when possible, and prevention is key.[823]
- Mouth care: an important part of overall patient care in hospitalized patients who are ventilated or nonventilated and those undergoing step-down or end-of-life care.[824]
- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia or depression as appropriate.[87]

Venous thromboembolism prophylaxis

- Assess the risk of bleeding as soon as possible after admission, or by the time of the first consultant review, using a suitable risk assessment tool.[20]
- Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalized adults and adolescents, provided there are no contraindications.[87] [19] [825] [826]
  - In the UK, the National Institute for Health and Care Excellence recommends starting as soon as possible (within 14 hours of admission) in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk, and continuing for a minimum of 7 days including after discharge.[20]
  - In children, the indications for venous thromboembolism prophylaxis should be the same as those for children without COVID-19.[19]
- Low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options for standard thromboprophylaxis.[87]
  - In the UK, the National Institute for Health and Care Excellence recommends low molecular weight heparin first-line, with fondaparinux or unfractionated heparin reserved for patients who cannot have low molecular weight heparin.[20]
  - In the US, the National Institutes of Health guidelines panel recommends parenteral over oral anticoagulants and, when heparin is used, low molecular weight heparin is preferred over unfractionated heparin. The panel recommends against the use of therapeutic-dose oral anticoagulants, except in the context of a clinical trial.[19]
  - Unfractionated heparin is contraindicated in patients with severe thrombocytopenia and patients with a history of heparin-induced thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia. Mechanical thromboprophylaxis (e.g., intermittent pneumatic compression devices) is recommended if anticoagulation is contraindicated or not available.[826] [827]
  - A retrospective observational study found that enoxaparin is associated with lower 28-day mortality, lower rates of bleeding events, lower intensive care admission rates, and shorter
hospital stays compared with unfractionated heparin; however, the study had important limitations and further research is required.[828]

• Avoid direct oral anticoagulants in the absence of an evidence-based indication for oral anticoagulation. An open-label, multicenter, randomized controlled trial found that in-hospital therapeutic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban until day 30 did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation among hospitalized patients with an elevated D-dimer level.[829]

• The optimal dose is yet to be determined. Standard prophylaxis doses are generally recommended across most guidelines over intermediate- or full treatment-dose regimens in patients without an established indication for higher-dose anticoagulation.[830] However, this recommendation varies and you should consult your local guidelines.

  • The World Health Organization recommends standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing in patients without an established indication for higher-dose anticoagulation.[87]
  • In the UK, the National Institute for Health and Care Excellence recommends a prophylactic dose of a low molecular weight heparin for a minimum of 7 days (including after discharge) in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk. A treatment dose of a low molecular weight heparin for 14 days or until discharge (whichever is sooner) may be considered in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk; however, this is a conditional recommendation only. The decision should be carefully considered, and choice of the most appropriate dose regimen should be guided by bleeding risk, clinical judgment, and local protocols. For those who do not need supplemental oxygen, follow standard VTE prophylaxis guidelines.[20]
  • In the US, the National Institutes of Health guidelines panel recommends prophylactic-dose heparin (low molecular weight heparin preferred over unfractionated heparin) for patients who are hospitalized but do not require supplemental oxygen, and therapeutic-dose heparin for patients who have a D-dimer level above the upper limit of normal, require low-flow oxygen, and have no increased bleeding risk. Treatment should continue for 14 days or until hospital discharge, whichever comes first. The panel recommends using prophylactic-dose heparin for patients who are not administered therapeutic heparin, unless a contraindication exists.[19]
  • Dose adjustments may be required in patients with extremes of body weight or renal impairment.[20]

• Evidence supports the use of lower-dose anticoagulant regimens.

• A Cochrane review found that higher-dose regimens resulted in little to no difference in all-cause mortality compared with lower-dose regimens in hospitalized patients; however, higher-dose regimens were associated with an increased risk of minor bleeding up to 30 days (high-certainty evidence). Higher-dose anticoagulants probably reduce pulmonary embolism and slightly increase major bleeding compared with lower-dose regimens up to 30 days (moderate-certainty evidence). Higher-dose anticoagulants may result in little or no difference in deep vein thrombosis, stroke, major adverse limb events, myocardial infarction, atrial fibrillation, or thrombocytopenia compared with lower-dose regimens up to 30 days.
(low-certainty evidence). Anticoagulants may reduce all-cause mortality compared with no anticoagulants, but the evidence is very uncertain.[831]

- For patients who are already on an anticoagulant for another underlying condition, continue the patient’s current medication and therapeutic dose unless contraindicated by a change in clinical circumstances.[19] [20] Consider switching to low molecular weight heparin if the patient’s clinical condition is deteriorating and the patient is not currently on low molecular weight heparin.[20]

  - A systematic review and meta-analysis found that the use of oral anticoagulation prior to hospital admission appeared to be ineffective at reducing the risk of intensive care unit admission and mortality; however, the review acknowledged that further trials are needed.[832]
  - A population-based cohort study found that people with atrial fibrillation and a low baseline risk of stroke who were taking oral anticoagulation had a marginally lower risk of COVID-19-related mortality compared with people not taking oral anticoagulation. However, it was not clear whether the association was causal or due to other differences between the groups.[833]

- Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected.[87]

  - If the patient’s clinical condition changes, assess the risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.[20]
  - Continue anticoagulation until hospital discharge.[87] Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients.[19] [825] [826] Ensure patients who require VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.[20]

  - A cohort study of nearly 3000 patients found that patients who had a history of venous thromboembolism, peak D-dimer >3 micrograms/mL, and predischARGE C-reactive protein >10 mg/dL were at high risk of experiencing new-onset venous thromboembolism post discharge, and these patients may benefit from post-discharge anticoagulation.[834]
  - A randomized controlled trial found that rivaroxaban for 35 days after hospital discharge improved clinical outcomes (reduction in thrombotic events) in high-risk patients compared with no extended thromboprophylaxis; however, further research is required.[835]

- There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulation in hospitalized patients with COVID-19.[836]

  - A systematic review and meta-analysis found that the pooled odds of mortality between anticoagulated and nonanticoagulated hospitalized patients were similar, but lower in the standard prophylactic-dose group. Prophylactic-dose anticoagulation significantly decreased the odds of in-hospital death by 17% compared with no anticoagulation. Mortality increased in the intermediate- to therapeutic-dose group with an increased risk of major bleeding.[837]
  - Clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[825]

### Antimicrobials

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• Do not offer antibiotics for preventing or treating pneumonia if SARS-CoV-2, another virus, or a fungal infection is likely to be the cause.[20] There is insufficient evidence to recommend empiric broad-spectrum antibiotics in the absence of another indication.[19]

• Consider empiric antibiotics if there is clinical suspicion of secondary bacterial infection. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria (or within 4 hours of establishing a diagnosis of secondary bacterial pneumonia); do not wait for microbiology results. Base the regimen on the clinical diagnosis (e.g., community-acquired pneumonia, hospital-acquired pneumonia, sepsis), local epidemiology and susceptibility data, and local treatment guidelines.[87] [19] [20]

• Consider seeking specialist advice for people who: are immunocompromised; have a history of infection with resistant organisms; have a history of repeated infective exacerbations of lung disease; are pregnant; or are receiving advanced respiratory or organ support. Seek specialist advice if there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic, or there is clinical or microbiologic evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.[20]

• Reassess antibiotic use daily. De-escalate empiric therapy on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching from intravenous to oral therapy. Duration of treatment should be as short as possible (e.g., 5 to 7 days). Antibiotic stewardship programs should be in place.[87]

• A meta-analysis found that the prevalence of antibiotic prescribing in patients with COVID-19 was 75%, which is significantly higher than the estimated prevalence of bacterial coinfection. Therefore, unnecessary antibiotic use is likely to be high in these patients.[838]

• Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.[87] The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection. Start empiric treatment with oseltamivir in hospitalized patients who are suspected of having either or both infections as soon as possible without waiting for influenza test results. Antiviral therapy can be stopped once influenza has been ruled out.[19]

Corticosteroids

• The WHO strongly recommends systemic corticosteroid therapy (low-dose intravenous or oral dexamethasone or hydrocortisone) for 7 to 10 days in adults with severe disease.[21] [795] [796] [839] [840]

• This recommendation is based on two meta-analyses that pooled data from eight randomized trials (over 7000 patients), including the UK RECOVERY trial.
• Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe disease.
• There is no evidence directly comparing dexamethasone and hydrocortisone.
• The harms of treatment in this context are considered to be minor.
• It is unclear whether these recommendations can be applied to children or those who are immunocompromised.

• In the UK, the National Institute for Health and Care Excellence recommends offering dexamethasone (or an alternative such as hydrocortisone or prednisone when dexamethasone cannot be used or is unavailable) to people who need supplemental oxygen to meet their
prescribed oxygen saturation levels, or who have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it.

- Treatment is for up to 10 days unless there is a clear indication to stop early.[20]
- In the US, the National Institutes of Health guidelines panel recommends dexamethasone, either alone or in combination with remdesivir, in hospitalized adults who require supplemental oxygen.

- Alternative corticosteroids may be used in situations where dexamethasone is not available.
- It is not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., via a nasal cannula only). Use of dexamethasone for the treatment of severe disease in children who are profoundly immunocompromised has not been evaluated, may be harmful, and therefore should be considered only on a case-by-case basis.[19]
- The Infectious Diseases Society of America supports the use of dexamethasone in hospitalized patients with severe disease.[510]
- Moderate- and low-certainty evidence supports the use of corticosteroids in hospitalized patients.

  - A Cochrane review found that systemic corticosteroids probably slightly reduce all-cause mortality in hospitalized patients with symptomatic disease. Most participants in the studies were treated with noninvasive or invasive mechanical ventilation. Low-certainty evidence suggests that there may also be a reduction in ventilator-free days; however, the current evidence remains uncertain due to methodological limitations. Evidence of an increased risk of mortality in symptomatic hospitalized patients without any need for additional oxygen was limited by a lack of statistical significance. It is unknown which systemic corticosteroid is most effective.[841]

  - Monitor patients for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.[19]

Antivirals

- There are conflicting recommendations across international guidelines about the use of the intravenous antiviral agent remdesivir in patients with severe disease. Consult your local guidance for more information.
- In the UK, the National Institute for Health and Care Excellence recommends considering remdesivir in hospitalized adults and children ≥12 years of age (weighing ≥40 kg) who require low-flow supplemental oxygen.[20]

  - Limited evidence suggests that remdesivir probably reduces the risk of death in hospitalized patients who need low-flow supplemental oxygen (moderate certainty). This is likely because it is being given early in the disease course.

- In the US, the National Institutes of Health guidelines panel recommends remdesivir in hospitalized adults who require supplemental oxygen. It may be given alone (e.g., for patients who require minimal supplemental oxygen) or in combination with dexamethasone (e.g., for patients who require increasing amounts of supplemental oxygen).[19]

  - The panel recommends remdesivir in hospitalized children ages ≥12 years who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen.
• The panel recommends remdesivir in hospitalized children ages ≥16 years who have an emergent or increasing need for supplemental oxygen, regardless of whether they have risk factors for severe disease.
• The panel recommends considering remdesivir in hospitalized children of all ages who have an emergent or increasing need for supplemental oxygen, in consultation with a pediatric infectious disease specialist.
• The Infectious Diseases Society of America supports the use of remdesivir in hospitalized patients with severe disease who require oxygen.\[510\]
• Remdesivir is approved in pediatric patients ≥28 days of age (weighing at least 7 lbs [3 kg]) in the US.\[807\]

  - The World Health Organization recommends against the use of remdesivir in hospitalized patients in addition to standard care, regardless of disease severity.\[21\] \[795\] \[796\] \[842\]

  - This weak or conditional recommendation is based on a systematic review and network meta-analysis of four randomized trials with 7333 hospitalized patients, and included the ACTT-1 trial and preliminary results from the WHO Solidarity trial. At the time of publication, there was no evidence that remdesivir improved patient outcomes such as time to clinical improvement, the need for mechanical ventilation, or mortality. However, the meta-analysis did not prove that remdesivir had no benefit.
  
  - Updated results from the WHO Solidarity trial published in May 2022 found that remdesivir may have a small effect against death and/or progression to ventilation. Overall, 14.5% of patients receiving remdesivir died compared with 15.6% in the control group. However, remdesivir had no significant effect on patients who were already being ventilated. In patients who were already ventilated, 42.1% of patients receiving remdesivir died compared with 38.5% in the control group. In patients who were not already ventilated, 11.9% of patients receiving remdesivir died compared with 13.5% in the control group, while 14.1% versus 15.7% progressed to ventilation.\[843\]
  
  - This recommendation is currently being reviewed, with an updated recommendation expected soon.

  - Moderate-certainty evidence does not support the use of remdesivir in hospitalized patients.

    - A Cochrane review found that remdesivir probably has little or no effect on 28-day all-cause mortality in hospitalized patients compared with placebo or usual care (moderate certainty). Effects on clinical improvement or worsening were uncertain. There were insufficient data available to examine the effect of remdesivir on mortality across subgroups defined by respiratory support at baseline.\[844\]

  - The recommended treatment course is 5 days or until hospital discharge, whichever comes first.\[19\]

  - Evidence does not suggest any greater benefit with a 10-day course of remdesivir compared with a 5-day course, but suggests an increased risk of harm.\[20\] However, some experts may recommend a 10-day course in patients who have not shown substantial clinical improvement by day 5.\[19\]

  - There may be no benefit in completing the full course of remdesivir if the patient progresses.\[20\] However, US guidelines recommend completing the full treatment course
Interleukin-6 (IL-6) inhibitors

- The WHO strongly recommends an IL-6 inhibitor (tocilizumab or sarilumab), in combination with a systemic corticosteroid and initiated at the same time, in patients with severe disease.[21] [795] [796]
  
  - IL-6 inhibitors are typically administered as a single intravenous dose; however, a second dose may be administered 12 to 48 hours after the first dose if the clinical response is inadequate.
  - This recommendation is based on high-certainty evidence that shows IL-6 inhibitors reduce mortality and the need for mechanical ventilation, and low-certainty evidence that suggests that IL-6 inhibitors may also reduce the duration of mechanical ventilation and hospitalization. The evidence regarding the risk of severe adverse events is uncertain.
  - The applicability of this recommendation to children is currently uncertain.
  - This recommendation is based on data from the UK RECOVERY and REMAP-CAP trials.[845] [846]
  
  - In the UK, the National Institute for Health and Care Excellence recommends a single dose of tocilizumab in hospitalized adults.[20]
    
    - Patients must meet the following conditions: they are having or have completed a course of corticosteroids such as dexamethasone (unless they cannot have corticosteroids); they have not had another IL-6 inhibitor during this admission; there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab; AND they either need supplemental oxygen and have a C-reactive protein level of ≥75 mg/L, OR they are within 48 hours of starting HFNO, continuous positive airway pressure, noninvasive ventilation, or invasive mechanical ventilation.
    - Consider tocilizumab for children and young people who have severe disease or pediatric inflammatory multisystem syndrome only if they are ages 1 year and over, and only in the context of a clinical trial.
    - Sarilumab may be considered an alternative option in adults only if tocilizumab cannot be used or is unavailable (use the same eligibility criteria as those for tocilizumab).
  
  - In the US, the National Institutes of Health guidelines panel recommends tocilizumab (or sarilumab if tocilizumab is not available or not feasible to use) for patients on a corticosteroid with rapidly increasing oxygen needs and systemic inflammation.[19] The Infectious Diseases Society of America recommends considering tocilizumab in hospitalized adults with progressive severe disease who have elevated markers of systemic inflammation, in addition to standard of care (i.e., corticosteroids), rather than standard of care alone. Sarilumab may be used if tocilizumab is not available.[510]
    
    - IL-6 inhibitors and Janus kinase inhibitors inhibitors (see below) are viewed as alternatives to each other and should not be administered together. Both drug classes prevent the dysregulated production of proinflammatory cytokines. There is potential for an additive risk of infection.
    - Evidence supports the use of these drugs.
• A Cochrane review found that tocilizumab reduced all-cause mortality at day 28, and probably resulted in fewer serious adverse events compared with standard care alone or placebo. The evidence suggests uncertainty around the effect on mortality after day 60. However, tocilizumab probably results in little or no increase in clinical improvement at day 28 (i.e., hospital discharge or improvement measured by trialist-defined scales). The impact of tocilizumab on other outcomes is uncertain. Evidence for an effect of sarilumab is uncertain.[847]

• A living systematic review and network meta-analysis found that IL-6 inhibitors are likely to reduce the need for mechanical ventilation (moderate-certainty evidence) and may reduce the duration of hospitalization (low-certainty evidence) compared with standard care.[848][849]

• A meta-analysis of approximately 20,000 patients from 45 randomized trials found that tocilizumab (in combination with corticosteroids) probably reduces mortality in people with severe or critical disease, and sarilumab (in combination with corticosteroids) could reduce mortality. The available evidence suggests that tocilizumab and sarilumab could be similarly effective. These drugs may not be beneficial when used without corticosteroids.[850]

Janus kinase (JAK) inhibitors

• The WHO strongly recommends a JAK inhibitor (baricitinib), in combination with a systemic corticosteroid and initiated at the same time, in patients with severe disease.[21][795][796]

  • JAK inhibitors are administered orally. The treatment duration is 14 days or until hospital discharge, whichever is first.
  • This recommendation is based on moderate-certainty evidence that baricitinib probably reduces mortality and duration of mechanical ventilation, and high-certainty evidence that baricitinib reduces length of hospital stay.
  • The applicability of this recommendation to children is currently uncertain.
  • Other drugs in this class include tofacitinib and ruxolitinib. The WHO recommends against using these drugs unless baricitinib or IL-6 inhibitors are not available as the effects of tofacitinib or ruxolitinib on mortality, need for mechanical ventilation, and hospital length of stay remain uncertain and more trial evidence is needed.

• In the UK, the National Institute for Health and Care Excellence recommends baricitinib in hospitalized adults who: need supplemental oxygen, and are having or have completed a course of corticosteroids (unless contraindicated), and have no evidence of infection (other than SARS-CoV-2) that might be worsened by baricitinib.[20]

  • Baricitinib may also be considered in children ≥2 years of age provided they meet the same criteria.
  • In the US, the National Institutes of Health guidelines panel recommends baricitinib (or tofacitinib if baricitinib is not available or not feasible to use) in patients on a corticosteroid with rapidly increasing oxygen needs and systemic inflammation.[19]
  • The Infectious Diseases Society of America suggests baricitinib (in combination with a corticosteroid) in hospitalized adults with severe disease. The guideline panel suggests baricitinib with remdesivir, rather than remdesivir alone, in patients who cannot receive a corticosteroid because of a contraindication. The panel suggests tofacitinib in
hospitalized adults with severe disease who are not on noninvasive or invasive mechanical ventilation.[510]

- JAK inhibitors and IL-6 inhibitors (see above) are viewed as alternatives to each other and should not be administered together. Both drug classes prevent the dysregulated production of proinflammatory cytokines. There is potential for an additive risk of infection.
- Evidence supports the use of these drugs.
  - A living systematic review and network meta-analysis found that JAK inhibitors may reduce the need for mechanical ventilation (low-certainty evidence) and probably reduce the duration of mechanical ventilation (moderate-certainty evidence) compared with standard care.[848] [849]
  - A meta-analysis that included four randomized controlled trials and 1300 participants found that treatment with a JAK inhibitor in addition to standard of care reduced the risk of death by 43%, and mechanical ventilation or extracorporeal membrane oxygenation by 36% compared with control.[851]
  - A systematic review and meta-analysis that included 12 articles (two double-blind randomized trials, four nonrandomized clinical trials, and six observational studies) and 3500 participants found that baricitinib reduced the rate of intensive care admission, requirement for invasive ventilation, and mortality.[852]

Monoclonal antibodies

- Monoclonal antibodies are authorized for use in some countries; however, availability and indications vary between countries. Consult your local guidance for more information.
  - Options may include sotrovimab and casirivimab/imdevimab, and bamlanivimab/etesevimab, depending on your location.
- Choice of monoclonal antibody depends on availability, as well as clinical and contextual factors including emerging information about efficacy with different variants.[19] [20] [21]
  - Preclinical evidence has emerged suggesting that casirivimab/imdevimab and bamlanivimab/etesevimab lack neutralization activity against the Omicron variant in vitro. Sotrovimab appears to retain activity against Omicron; however, sotrovimab is not active against the Omicron BA.2 subvariant.
  - Recommendations for monoclonal antibodies in patients with severe disease differ from the recommendations in patients with mild to moderate disease.
  - Logistical or supply constraints may make patient triage for monoclonal antibody treatment necessary.
- The World Health Organization recommends casirivimab/imdevimab (but not sotrovimab) for patients with severe disease with a seronegative status (i.e., no detectable SARS-CoV-2 antibodies).[21] [795] [796]
  - Casirivimab/imdevimab should only be used where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e., excluding Omicron).
  - Casirivimab/imdevimab probably reduces mortality and possibly reduces the need for mechanical ventilation in patients who are seronegative based on moderate- and low-
certainty evidence, respectively. Sotrovimab did not demonstrate efficacy in seronegative patients with severe/critical disease in one randomized controlled trial.

- Treatment is in addition to the current standard of care.
- The applicability of this recommendation to children is currently uncertain.

- In the UK, the National Institute for Health and Care Excellence recommends casirivimab/imdevimab in hospitalized patients ≥12 years of age who are seronegative, provided they meet all of the eligibility criteria and none of the exclusion criteria (see guidance for more information).[20]

- Do not offer casirivimab/imdevimab to patients who are known or suspected to have infection caused by an Omicron variant. Only offer casirivimab/imdevimab to patients when the infection is known to be caused by a variant susceptible to casirivimab/imdevimab.
- A UK clinical commissioning policy also recommends sotrovimab for hospital-onset infection in certain patients (see guidance for more information).[853]

- In the US, the National Institutes of Health guidelines panel states that casirivimab/imdevimab and sotrovimab and bamlanivimab/etesevimab are not currently authorized for use in hospitalized patients with severe disease.[19]

- However, they may be available through expanded access programs for patients who are hospitalized with severe disease who have not developed an antibody response or who are not expected to mount an effective immune response (e.g., immunocompromised patients).

- Monoclonal antibodies are administered by intravenous infusion.

- Casirivimab/imdevimab is also available in a subcutaneous formulation, but intravenous administration is recommended. However, if intravenous infusions are not feasible or would cause a delay in treatment, subcutaneous administration may be considered.[19]

- Evidence for the use of monoclonal antibodies in hospitalized patients is uncertain.

- A Cochrane review found that casirivimab/imdevimab probably has no effect on mortality, progression to invasive mechanical ventilation, and 30-day hospital discharge in hospitalized patients (moderate-certainty evidence). Bamlanivimab may have little to no effect on efficacy outcomes when compared with placebo, but it may increase the occurrence of severe symptoms and adverse events (low-certainty evidence).[806]
- The UK RECOVERY trial found that casirivimab/imdevimab reduced 28-day mortality in hospitalized patients who were seronegative at baseline, but not in those who were seropositive at baseline.[854]

Monitor

- Monitor patients closely for signs of clinical deterioration, and respond immediately with appropriate supportive care interventions.[87]

Discharge and rehabilitation

- Routinely assess older patients for mobility, functional swallow, cognitive impairment, and mental health concerns, and based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[87]

Palliative care
• Palliative care interventions should be made accessible at each institution that provides care for patients with COVID-19. Identify whether the patient has an advance care plan and respect the patient’s priorities and preferences when formulating the patient’s care plan.[87]

• There are a lack of data on palliative care in patients with COVID-19. However, a rapid systematic review of pharmacologic strategies used for palliative care in these patients, the first international review of its kind, found that a higher proportion of patients required continuous subcutaneous infusions for medication delivery than is typically seen in the palliative care population. Modest doses of commonly used end-of-life medications were required for symptom control. However, these findings should be interpreted with caution due to the lack of data available.[855]

• Follow local palliative care guidelines.

Critical COVID-19

Patients with critical disease (i.e., presence of acute respiratory distress syndrome, sepsis, or septic shock) should be admitted or transferred to an intensive/critical care unit. Use existing care bundles (i.e., three or more evidence-informed practices delivered together and consistently to improve care), chosen locally by the hospital or intensive care unit and adapted as necessary for local circumstances.[87]

Overall, 19% of hospitalized patients required noninvasive ventilation, 17% required intensive care, 9% required invasive ventilation, and 2% required extracorporeal membrane oxygenation.[676] The rate of intensive care admission varies between studies; however, a meta-analysis of nearly 25,000 patients found that the admission rate was 32%, and the pooled prevalence of mortality in patients in the intensive care unit was 39%.[856] Another more recent meta-analysis found the mortality rate in patients in the intensive care unit to be 35.5%. [857] The most common reasons for intensive care unit admission were hypoxemic respiratory failure leading to mechanical ventilation and hypotension.[858]

Patients admitted to intensive care units were older, were predominantly male, and had a median length of stay of 23 days (range 12-32 days).[859] The strongest risk factors for critical illness were oxygen saturation <88%; elevated serum troponin, C-reactive protein, and D-dimer; and, to a lesser extent, older age, body mass index >40, heart failure, and male sex.[860] The most common risk factors for intensive care unit mortality were invasive mechanical ventilation, acute kidney injury, and acute respiratory distress syndrome.[861]

Risk factors for intensive care admission in children include age <1 month, male sex, preexisting medical conditions, and presence of lower respiratory tract infection signs or symptoms at presentation.[862] The majority of children who required ventilation had underlying comorbidities, most commonly cardiac disease.[863]

Location of care

• Manage patients in an intensive/critical care unit under the guidance of a specialist team.[87]
• Discuss the risks, benefits, and potential outcomes of treatment options with patients and their families, and allow them to express preferences about their management. Take their wishes and expectations into account when considering the ceiling of treatment. Use decision support tools if available. Put treatment escalation plans in place, and discuss any existing advance care
plans or advance decisions to refuse treatment with patients who have preexisting advanced comorbidities.[20]

HFNO or noninvasive ventilation

- The World Health Organization recommends considering a trial of HFNO or noninvasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in selected patients with mild acute respiratory distress syndrome (ARDS).
  - Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require HFNO or noninvasive ventilation.[87]
  - In the UK, the National Institute for Health and Care Excellence recommends CPAP in patients with hypoxemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of ≥0.4 (40%), and escalation to invasive mechanical ventilation would be an option but it is not immediately needed or it is agreed that respiratory support should not be escalated beyond CPAP.[20]

- Ensure there is access to critical care providers for advice, regular review, and prompt escalation of treatment if needed, and regular assessment and management of symptoms alongside noninvasive respiratory support.
- Consider using HFNO for people when: they cannot tolerate CPAP but need humidified oxygen at high flow rates; maximal conventional oxygen is not maintaining their target oxygen saturations and they do not need immediate invasive mechanical ventilation or escalation to invasive mechanical ventilation is not suitable, and CPAP is not suitable; or they need a break from CPAP (e.g., mealtimes, skin pressure relief, mouth care), need humidified oxygen or nebulizers (or both), or need weaning from CPAP.
- Do not routinely offer HFNO as the main form of respiratory support for people with respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate.
- Optimize pharmacologic and nonpharmacologic management strategies in people who need noninvasive respiratory support.
- Consider awake prone positioning for hospitalized patients who are not intubated and have higher oxygen needs.

- In the US, the National Institutes of Health guidelines panel recommends HFNO over noninvasive ventilation in patients with acute hypoxemic respiratory failure despite conventional oxygen therapy.[19]
  - The panel recommends a closely monitored trial of noninvasive ventilation if HFNO is not available.
  - A trial of awake prone positioning is recommended in patients with persistent hypoxemia who require HFNO and for whom endotracheal intubation is not indicated. The panel recommends against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and invasive mechanical ventilation.

- Evidence for noninvasive ventilation is limited.
• There is no certain evidence that noninvasive respiratory support increases or decreases mortality in patients with COVID-19 acute respiratory failure.[864]

• Limited evidence suggests that noninvasive ventilation reduces the need for intubation, improves resource utilization, may be associated with better outcomes, and is safe.[865]

• Indirect and low-certainty evidence suggests that noninvasive ventilation probably reduces mortality, similar to invasive mechanical ventilation, but may increase the risk of viral transmission. HFNO may reduce mortality compared with no HFNO.[866] [867]

• HFNO was superior to noninvasive ventilation for acute respiratory failure in terms of decreasing mortality. However, there was no significant difference in intubation rates and length of hospital stay between the two groups.[868] [869]

• The RECOVERY-RS trial (an open-label, multicenter, adaptive randomized controlled trial) found that CPAP reduced the need for invasive mechanical ventilation in adults admitted to hospital with acute respiratory failure. Neither CPAP nor HFNO reduced mortality when compared with conventional oxygen therapy.[870]

• Another randomized controlled trial found that treatment with HFNO reduced the likelihood of invasive mechanical ventilation and decreased the time to clinical recovery compared with conventional low-flow oxygen therapy in patients with severe disease.[871]

• Awake prone positioning of nonintubated patients was associated with improvement in oxygen variables (PaO₂/FiO₂, PaO₂, and SpO₂), respiratory rate, rate of intubation (particularly among those who required advanced respiratory support and those in intensive care unit settings), and mortality. However, evidence is limited.[817] [818] [819] [820]

• Airborne precautions are recommended for these interventions (including bubble CPAP) due to uncertainty about the potential for aerosolization.[87]

• CPAP and HFNO do not appear to be associated with significant additional air or surface viral contamination compared with supplemental oxygen.[872]

• Patients with hypercapnia, hemodynamic instability, multi-organ failure, or abnormal mental status should generally not receive HFNO, although emerging data suggests that it may be safe in patients with mild to moderate and nonworsening hypercapnia. Patients with hypoxemic respiratory failure and hemodynamic instability, multi-organ failure, or abnormal mental status should not receive these treatments in place of other options such as invasive ventilation.[87]

• Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions they require urgent endotracheal intubation.[87] [816]

• More detailed guidance on the management of ARDS in COVID-19 is beyond the scope of this topic; consult a specialist for further guidance.

**Mechanical ventilation**

• Consider endotracheal intubation and invasive mechanical ventilation in patients who are acutely deteriorating despite advanced oxygen/noninvasive ventilatory support measures.[87] [19]

• Use of mechanical ventilation in COVID-19 patients carries a high risk of mortality. Mortality is highly variable across studies, ranging between 21% and 100%. An overall in-hospital mortality risk ratio of 0.70 has been reported based on random-effect pooled estimates. However, it is important to note that outcomes appear to have improved as the pandemic has progressed.[873]
Coronavirus disease 2019 (COVID-19) Management

• Endotracheal intubation should be performed by an experienced provider using airborne precautions.[87] Intubation by video laryngoscopy is recommended if possible.[19] Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require preoxygenation with 100% FiO₂ for 5 minutes.[87]

• Mechanically ventilated patients with ARDS should receive a lung-protective, low tidal volume/low inspiratory pressure ventilation strategy (lower targets are recommended in children). A higher positive end-expiratory pressure (PEEP) strategy is preferred over a lower PEEP strategy in moderate to severe ARDS. However, individualization of PEEP, where the patient is monitored for beneficial or harmful effects and driving pressure during titration with consideration of the risks and benefits of PEEP titration, is recommended.[87][19][816]

• Although some patients with COVID-19 pneumonia meet the criteria for ARDS, there is some discussion about whether COVID-19 pneumonia is its own specific disease with atypical phenotypes. Anecdotal evidence suggests that the main characteristic of the atypical presentation is the dissociation between well-preserved lung mechanics and the severity of hypoxemia.[874][875][876][877][878][879] However, this approach has been criticized.[880][881] Results from three large observational cohort studies with data from critically ill patients with acute respiratory failure found that COVID-19-related ARDS had no consistent respiratory subphenotype at baseline (start of invasive ventilation). However, time-dependent analysis showed that two subphenotypes developed during the first 4 days of mechanical ventilation. Patients with an upward trajectory of ventilatory ratio had a higher risk of venous thrombotic events, more frequently developed acute kidney injury, required longer invasive mechanical ventilation, and had higher mortality.[882]

• It has been argued that an evidence-based approach extrapolating data from ARDS not related to COVID-19 is the most reasonable approach for intensive care of COVID-19 patients.[883] As a consequence of this, some clinicians have warned that protocol-driven ventilator use may be causing lung injury in some patients, and that ventilator settings should be based on physiologic findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.[874]

• PEEP should always be carefully titrated.[884]

• Consider prone ventilation in patients with severe ARDS for 12 to 16 hours per day. Pregnant women in the third trimester may benefit from being placed in the lateral decubitus position. Caution is required in children.[87][19][816] Longer durations may be feasible in some patients.[885]

• Lung recruitment maneuvers are suggested, but staircase recruitment maneuvers are not recommended.[19][816]

• More detailed guidance on the management of ARDS in COVID-19, including sedation and the use of neuromuscular blockade during ventilation, is beyond the scope of this topic; consult a specialist for further guidance.

Inhaled pulmonary vasodilator

• Consider a trial of an inhaled pulmonary vasodilator in adults who have severe ARDS and hypoxemia despite optimizing ventilation. Taper off if there is no rapid improvement in oxygenation.[19][816]

Extracorporeal membrane oxygenation

• Consider extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[87][816][886]
• There is insufficient evidence to recommend either for or against the routine use of ECMO.[19]

• A systematic review and meta-analysis found that in-hospital mortality in adults receiving ECMO was 39%, and the risk of mortality was higher when compared with influenza patients on ECMO (44% versus 38%).[887]

• A registry-based cohort study found that ECMO was associated with a 7.1% reduction in mortality in selected adults (i.e., PaO₂/FiO₂ <80 mmHg) with COVID-19-associated respiratory failure, compared with conventional mechanical ventilation without ECMO. It was most effective in patients ages <65 years and those with a PaO₂/FiO₂ <80 mmHg or with driving pressures >15 cm H₂O during the first 10 days of mechanical ventilation.[888]

• Single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure.[889]

• There is a risk of neurologic complications (e.g., intracranial hemorrhage, ischemic stroke, and hypoxic ischemic brain injury) in patients on ECMO.[890]

Management of septic shock/sepsis

• The management of sepsis and septic shock in patients with COVID-19 is beyond the scope of this topic. See the Complications section.

Symptom management and supportive care

• Consider fluid and electrolyte management, antimicrobial treatment, and symptom management as appropriate (see Severe COVID-19 above).

Venous thromboembolism prophylaxis

• Recommendations for patients with critical disease may differ from those for severe disease (see above). Consult your local guidelines.

• In the UK, the National Institute for Health and Care Excellence recommends a prophylactic dose of a low molecular weight heparin to young people and adults who need HFNO, CPAP, noninvasive ventilation, or invasive mechanical ventilation, and who do not have an increased bleeding risk. An intermediate or treatment dose of a low molecular weight heparin is only recommended in these patients as part of a clinical trial.[20]

• In the US, the National Institutes of Health guidelines panel recommends prophylactic-dose heparin (low molecular weight heparin preferred over unfractionated heparin) for patients who are receiving intensive care unit level of care (including patients receiving high-flow oxygen), unless there is a contraindication. The panel recommends against the use of intermediate-dose and therapeutic-dose anticoagulation in these patients, except in the context of a clinical trial. Patients who start on therapeutic-dose heparin while in a non-intensive care unit setting and then transfer to the intensive care unit should be switched from therapeutic to prophylactic-dose heparin unless venous thromboembolism is confirmed.[19]

• Some guidelines recommend that escalated doses can be considered in critically ill patients.[825] [891]

• Evidence is limited in patients with critical disease.
Management

A systematic review and meta-analysis of nearly 28,000 hospitalized patients found that both intermediate-dose and therapeutic-dose anticoagulation decreased the risk of thrombotic events in critically ill patients in the intensive care unit compared with prophylactic-dose anticoagulation, but these regimens were associated with an increased bleeding risk and unchanged in-hospital mortality.[892]

Corticosteroids

- The WHO strongly recommends systemic corticosteroid therapy (low-dose intravenous or oral dexamethasone or hydrocortisone) for 7 to 10 days in adults with critical disease.

- Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with critical disease. They also probably reduce the need for invasive ventilation.[21]

- There is also evidence that corticosteroids probably increase ventilator-free days (moderate certainty).[848] [849]

- In the US, the National Institutes of Health guidelines panel recommends dexamethasone (or a suitable alternative corticosteroid), either alone or in combination with remdesivir, in hospitalized patients who require high-flow oxygen or noninvasive ventilation. In patients who are on mechanical ventilation or ECMO, the panel recommends dexamethasone alone or in combination with tocilizumab for patients who are within 24 hours of admission to the intensive care unit. The panel recommends using dexamethasone in hospitalized children who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[19]

- A meta-analysis found an increased risk of VTE with corticosteroid administration in patients with critical disease. However, no definite findings were available due to the differing corticosteroid regimens and the heterogeneity of the studies.[893]

- See the corticosteroids section under Severe COVID-19 above for more information.

Antivirals

- There are conflicting recommendations across international guidelines about the use of the intravenous antiviral agent remdesivir. Remdesivir may increase the risk of death in critically ill patients, and currently only US guidelines recommend its use in select patients. Consult your local guidance for more information.

- In the US, the National Institutes of Health guidelines panel recommends remdesivir, in combination with dexamethasone, in hospitalized patients who require high-flow oxygen or noninvasive ventilation.[19]

- The panel does not recommend starting remdesivir in patients who require invasive mechanical ventilation or ECMO. However, the panel does recommend completing the full treatment course of remdesivir if the patient is started on it when they are on supplemental low-flow oxygen (see Severe COVID-19 above) and then progress to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation.
• The recommended treatment course is 5 days or until hospital discharge, whichever comes first.[19]

• Evidence does not suggest any greater benefit with a 10-day course of remdesivir compared with a 5-day course, but suggests an increased risk of harm.[20] However, some experts may recommend a 10-day course in patients who have not shown substantial clinical improvement by day 5.[19]

• In the UK, the National Institute for Health and Care Excellence recommends against the use of remdesivir in hospitalized patients on HFNO, continuous positive airway pressure, noninvasive mechanical ventilation, or invasive mechanical ventilation, except as part of a clinical trial.[20]

• Evidence shows that remdesivir may increase the risk of death in people who are on these interventions (moderate certainty).

• The World Health Organization recommends against the use of remdesivir in hospitalized patients in addition to standard care, regardless of disease severity. However, this recommendation is currently being reviewed, with an updated recommendation expected soon.[21] [795] [796] [842]

• See the antivirals section under Severe COVID-19 above for more information.

**IL-6 inhibitors**

• The WHO strongly recommends an IL-6 inhibitor, in combination with a systemic corticosteroid and initiated at the same time, in patients with critical disease.[21] [795] [796]

• In the US, the National Institutes of Health guidelines panel recommends adding tocilizumab to dexamethasone (or a suitable alternative corticosteroid) or dexamethasone plus remdesivir in patients who require noninvasive mechanical ventilation or HFNO and have been recently hospitalized (e.g., within 3 days) with rapidly increasing oxygen needs and systemic inflammation.[19]

• In patients who are on mechanical ventilation or ECMO, the panel recommends adding tocilizumab to dexamethasone for patients who are within 24 hours of admission to the intensive care unit.

• There is insufficient evidence for the panel to recommend either for or against the use of tocilizumab in hospitalized children.

• Sarilumab may be used as an alternative if tocilizumab is not available or it is not feasible to use it.

• The Infectious Diseases Society of America recommends considering tocilizumab in hospitalized adults with critical disease who have elevated markers of systemic inflammation, in addition to standard of care (i.e., corticosteroids), rather than standard of care alone. Sarilumab may be used if tocilizumab is not available.[510]

• See the IL-6 inhibitors section under Severe COVID-19 above for more information.

**Janus kinase (JAK) inhibitors**

• The WHO strongly recommends a JAK inhibitor (baricitinib), in combination with a systemic corticosteroid and initiated at the same time, in patients with critical disease.[21] [795] [796]

• In the UK, the National Institute for Health and Care Excellence recommends baricitinib in hospitalized adults who: need supplemental oxygen (or other respiratory support including HFNO, CPAP, noninvasive ventilation, or mechanical ventilation), and are having or have completed a
Management

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Course of corticosteroids (unless contraindicated), and have no evidence of infection (other than SARS-CoV-2) that might be worsened by baricitinib.[20]

- Baricitinib may also be considered in children ≥2 years of age provided they meet the same criteria.
- In the US, the National Institutes of Health guidelines panel recommends adding baricitinib to dexamethasone (or a suitable alternative corticosteroid) or dexamethasone plus remdesivir in patients who require noninvasive mechanical ventilation or HFNO and have been recently hospitalized with rapidly increasing oxygen needs and systemic inflammation.[19]
  - The panel recommends against the use of baricitinib in combination with tocilizumab except in the context of a clinical trial.
  - Tofacitinib may be used as an alternative if baricitinib is not available or it is not feasible to use it.
- Evidence to support the use of baricitinib in critically ill patients is emerging.
  - An exploratory, randomized, placebo-controlled trial found that baricitinib (in combination with standard of care, including corticosteroids) reduced 28-day all-cause mortality (19% absolute reduction) and 60-day all-cause mortality (17% absolute reduction) in critically ill hospitalized patients who were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation compared with placebo. Further phase 3 trials are needed to confirm these findings as this was a small sample.[894]
  - See the JAK inhibitors section under Severe COVID-19 above for more information.

Monoclonal antibodies

- Monoclonal antibodies are authorized for use in some countries; however, availability and indications vary between countries. Consult your local guidance for more information.
- The World Health Organization recommends casirivimab/imdevimab for patients with critical disease with a seronegative status (i.e., no detectable SARS-CoV-2 antibodies).[21] [795] [796]
  - Casirivimab/imdevimab should only be used where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e., excluding Omicron).
  - Casirivimab/imdevimab probably reduces mortality and possibly reduces the need for mechanical ventilation in patients who are seronegative based on moderate- and low-certainty evidence, respectively.
  - See the Monoclonal antibodies section under Severe COVID-19 above for more information.

Discharge and rehabilitation

- Routinely assess intensive care patients for mobility, functional swallow, cognitive impairment, and mental health concerns, and based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[87]

Palliative care

- Palliative care interventions should be made accessible at each institution that provides care for patients with COVID-19. Identify whether the patient has an advance care plan and respect the patient’s priorities and preferences when formulating the patient’s care plan.[87]
• There are a lack of data on palliative care in patients with COVID-19. However, a rapid systematic review of pharmacologic strategies used for palliative care in these patients, the first international review of its kind, found that a higher proportion of patients required continuous subcutaneous infusions for medication delivery than is typically seen in the palliative care population. Modest doses of commonly used end-of-life medications were required for symptom control. However, these findings should be interpreted with caution due to the lack of data available.\cite{855}

• Follow local palliative care guidelines.

Management of pregnant women

Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as midwifery and mental health and psychosocial support. A woman-centered, respectful, skilled approach to care is recommended.\cite{87} In women with severe or critical disease, the multidisciplinary team should be organized as soon as possible after maternal hypoxemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.\cite{895} There is significant heterogeneity in several aspects of management of pregnant women across clinical practice guidelines, especially regarding follow-up after infection and timing of delivery. However, there is a general agreement in the criteria for maternal hospitalization and mode of delivery.\cite{896}

Location of care

• Manage pregnant women in a healthcare facility, in a community facility, or at home. Women with suspected or confirmed mild disease may not require acute care in a hospital unless there is concern for rapid deterioration or an inability to return to hospital promptly.\cite{87} Follow local infection prevention and control procedures as for nonpregnant people.

• Consider home care in women with asymptomatic or mild illness, provided the patient has no signs of potentially severe illness (e.g., breathlessness, hemoptysis, new chest pain/pressure, anorexia, dehydration, confusion), no comorbidities, and no obstetric issues; the patient is able to care for herself; and monitoring and follow-up is possible. Otherwise, manage pregnant women in a hospital setting with appropriate maternal and fetal monitoring whenever possible.\cite{633} \cite{897}

• Postpone routine prenatal or postpartum health visits for women who are in home isolation and reschedule them after the isolation period is completed. Delivery of counseling and care should be conducted via telemedicine whenever possible. Counsel women about healthy diet, mobility and exercise, intake of micronutrients, smoking, and alcohol and substance use. Advise women to seek urgent care if they develop any worsening of illness or danger signs, or danger signs of pregnancy.\cite{87}

Prenatal corticosteroids

• Consider prenatal corticosteroids for fetal lung maturation in women who are at risk of preterm birth (24 to 37 weeks’ gestation). Caution is advised because corticosteroids could potentially worsen the maternal clinical condition, and the decision should be made in conjunction with the multidisciplinary team.\cite{633} \cite{897} \cite{898}
• The WHO recommends prenatal corticosteroids only when there is no clinical evidence of maternal infection and adequate childbirth and newborn care is available, and in women with mild COVID-19 after assessing the risks and benefits.[87]

• As corticosteroid therapy is recommended as part of the treatment strategy for COVID-19, the specific corticosteroid and dose may depend on whether corticosteroids are indicated for fetal lung maturity.[460]

Treatments

• There are limited data available on the management of pregnant women with COVID-19; however, pregnant women can generally be treated with the same supportive therapies detailed above, taking into account the physiologic changes that occur with pregnancy. It is important that pregnant women are not denied treatment inappropriately.[87] [899]

• Most clinical trials to date have excluded pregnant women. However, potentially effective treatments should not be withheld from pregnant women due to theoretical concerns about the safety of these therapeutic agents in pregnancy. Decisions should be made with a shared decision-making process between the patient and the clinical team.[19]

• Treatment with corticosteroids should be modified to use nonfluorinated glucocorticoids. IL-6 inhibitors, monoclonal antibodies, and antiviral therapies may be considered. VTE prophylaxis is important in pregnant women. They may also require respiratory support with oxygen, noninvasive ventilation, ventilation in a prone position, intubation and ventilation, and ECMO.[899] Safety of COVID-19 antivirals (e.g., remdesivir, nirmatrelvir/ritonavir, molnupiravir) in pregnancy has not been established.

VTE prophylaxis

• The National Institutes of Health recommends prophylactic dose anticoagulation in pregnant women who are hospitalized with severe disease, provided there are no contraindications to its use. There is currently insufficient evidence to recommend either for or against therapeutic anticoagulation for pregnant women in the absence of known venous thromboembolism. Anticoagulation during labor and delivery requires specialized care and planning, and should be managed in a similar way as for pregnant women with other conditions.[19]

• The Royal College of Obstetricians and Gynaecologists (RCOG) has also published guidance on the prevention of VTE in pregnant women.[460]

Labor and delivery

• Implement local infection prevention and control measures during labor and delivery. Screen birth partners for COVID-19 infection using the standard case definition.[87]

• Individualize mode of birth based on obstetric indications and the woman’s preferences. Vaginal delivery is preferred in women with confirmed infection to avoid unnecessary surgical complications. Induction of labor, interventions to accelerate labor and delivery, and cesarean delivery are generally only recommended when medically justified based on maternal and fetal condition. COVID-19 positive status alone is not an indication for cesarean section.[87] [633] [897]

• Delayed umbilical cord clamping (not earlier than 1 minute after birth) is recommended for improved maternal and infant health and nutrition outcomes. The risk of transmission via blood is thought to be minimal, and there is no evidence that delayed cord clamping increases the risk of viral transmission from the mother to the newborn.[87]
• Consider babies born to mothers with suspected or confirmed infection to be a person under investigation and isolate them from healthy newborns. Test them for infection 24 hours after birth, and again 48 hours after birth.[900]

Newborn care

• Experts are divided on separating mother and baby after delivery; make decisions on a case-by-case basis using shared-decision making.

  • A retrospective cohort analysis, the largest series to date, found no clinical evidence of vertical transmission in 101 newborns born to mothers with suspected or confirmed SARS-CoV-2 infection, despite most newborns rooming-in and direct breastfeeding practices. This suggests that separation may not be warranted and breastfeeding appears to be safe.[901]

  • The WHO recommends that mothers and infants should remain together unless the mother is too sick to care for her baby. Breastfeeding should be encouraged while applying appropriate infection prevention and control measures (e.g., performing hand hygiene before and after contact with the baby, wearing a mask while breastfeeding).[87]

  • The WHO advises that the benefits of breastfeeding outweigh the potential risks for transmission.[902]

  • Mother-to-infant transmission appears to be rare during rooming-in, provided that adequate droplet and contact precautions are taken.[903]

• The CDC recommends that temporary separation of a newborn from a mother with confirmed or suspected COVID-19 may be considered after weighing the risks and benefits as current evidence suggests the risk of a neonate acquiring infection from its mother is low; healthcare providers should respect maternal autonomy in the medical decision-making process. If separation is not undertaken, measures to minimize the risk of transmission should be implemented.[904]

  • A mother with confirmed infection should be counseled to take all possible precautions to avoid transmission to the infant during breastfeeding (e.g., hand hygiene, wearing a mask). Expressed milk should be fed to the newborn by a healthy caregiver.[905]

• The RCOG recommends that mothers with confirmed infection and healthy babies are kept together in the immediate postpartum period, provided they do not meet criteria for maternal critical care or additional neonatal care.[460]

  • Breastfeeding should be recommended to all women in line with usual guidance, and women should be supported to make an informed decision about how they feed their baby. Appropriate preventive precautions are recommended to limit transmission to the baby.

• The American Academy of Pediatrics (AAP) recommends that mothers and newborns may room-in, with appropriate infection prevention and control precautions, according to usual center practice.[900]

  • However, it may be appropriate to temporarily separate the mother and newborn (or to have the newborn cared for by noninfected caregivers in the mother’s room) when the mother is acutely ill with COVID-19 and cannot care for the infant in a safe way.

  • The AAP strongly supports breastfeeding as the best choice for feeding. Breast milk can be expressed after appropriate hygiene measures and fed by an uninfected caregiver. If the
mother chooses to breastfeed the infant themselves, appropriate prevention measures are recommended.

- After discharge, advise mothers with COVID-19 to practice prevention measures (e.g., hand hygiene, respiratory hygiene/mask) for newborn care until: they are afebrile for 24 hours without the use of antipyretics; at least 10 days have passed since symptoms first appeared (or 10 days since a positive test in asymptomatic women); and symptoms have improved.
- A newborn with documented infection but no symptoms requires close outpatient follow-up after discharge for 14 days after birth.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
### Acute (summary)

#### mild COVID-19

- **1st** consider home isolation
- **plus** monitoring
- **plus** symptom management and supportive care
- **adjunct** antipyretic/analgesic
- **adjunct** monoclonal antibody
- **adjunct** antiviral

#### moderate COVID-19

- **1st** consider home isolation or hospital admission
- **plus** monitoring
- **plus** symptom management and supportive care
- **adjunct** antibiotics
- **adjunct** antipyretic/analgesic
- **adjunct** monoclonal antibody
- **adjunct** antiviral

#### severe COVID-19

- **1st** hospital admission
- **plus** consider oxygen therapy
- **plus** symptom management and supportive care
- **plus** venous thromboembolism prophylaxis
- **plus** monitoring
- **adjunct** antibiotics
- **adjunct** corticosteroid
- **adjunct** antiviral
- **adjunct** interleukin-6 (IL-6) inhibitor
- **adjunct** Janus kinase (JAK) inhibitor
- **adjunct** treatment of coinfections
- **adjunct** antipyretic/analgesic
- **adjunct** monoclonal antibody
- **adjunct** experimental therapies
## Acute

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<th>Adjunct Plan for Discharge and Rehabilitation</th>
<th>Palliative Care</th>
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### Critical COVID-19

- **1st** intensive/critical care unit admission
- **Plus** symptom management and supportive care
- **Plus** venous thromboembolism prophylaxis
- **Plus** consider high-flow nasal oxygen or noninvasive ventilation
- **Plus** consider invasive mechanical ventilation
- **Adjunct** inhaled pulmonary vasodilator
- **Adjunct** extracorporeal membrane oxygenation
- **Adjunct** management of sepsis/septic shock
- **Adjunct** corticosteroid
- **Adjunct** antiviral
- **Adjunct** interleukin-6 (IL-6) inhibitor
- **Adjunct** Janus kinase (JAK) inhibitor
- **Adjunct** treatment of coinfections
- **Adjunct** monoclonal antibody
- **Adjunct** experimental therapies
- **Adjunct** plan for discharge and rehabilitation
- **Adjunct** palliative care
Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
Acute

mild COVID-19

1st consider home isolation

» Isolate patients with suspected or confirmed mild disease (i.e., symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia) and asymptomatic patients to contain virus transmission.[87]

» Manage patients in a healthcare facility, in a community facility, or at home. Home isolation can be considered in most patients, with telemedicine or remote visits as appropriate.[87][19] This decision requires careful clinical judgment and should be informed by an assessment of the patient’s home environment to ensure that: infection prevention and control measures and other requirements can be met (e.g., basic hygiene, adequate ventilation); the caregiver is able to provide care and recognize when the patient may be deteriorating; the caregiver has adequate support (e.g., food, supplies, psychological support); the support of a trained health worker is available in the community.[799] The location of care will depend on guidance from local health authorities and available resources.

» Pregnant women with suspected or confirmed mild disease may not require acute care in a hospital unless there is concern for rapid deterioration or an inability to return to hospital promptly.[87]

» Advise patients and household members to follow appropriate infection prevention and control measures:


## Acute

- Guidance on when to stop isolation varies widely across locations. Isolation periods may depend on various factors including vaccination status, circulating SARS-CoV-2 variants, and patient factors (e.g., immunocompetent/immunocompromised, asymptomatic/symptomatic, disease severity). The World Health Organization recommends discontinuing transmission-based precautions (including isolation) and releasing patients from the care pathway 10 days after positive test (asymptomatic patients), or 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms (symptomatic patients).[87] However, some countries now recommend isolation periods as short as 5 days to 7 days.[797] Consult your local public health guidance for more information.

### plus monitoring

Treatment recommended for ALL patients in selected patient group

- Closely monitor patients with risk factors for severe illness and counsel patients about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain).[87] [19]

- Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalized. Patient education and appropriate follow-up are required.[87]

### plus symptom management and supportive care

Treatment recommended for ALL patients in selected patient group

- Advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough.[20] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[800]

- Advise patients about adequate nutrition and appropriate rehydration. Advise patients to drink fluids regularly to avoid dehydration. Fluid intake needs can be higher than usual because of fever. However, too much fluid can worsen oxygenation.[87] [20]
Acute

» Advise patients to improve air circulation by opening a window or door.[20]

» Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[87]

» Consider treatment for olfactory dysfunction (e.g., olfactory training) if it persists beyond 2 weeks. There is no evidence to support the use of these treatments in patients with COVID-19.[801] A Cochrane review found there is very limited evidence regarding the efficacy of different interventions at preventing persistent olfactory dysfunction following infection. The only evidence available is for intranasal corticosteroids, and this is of very low certainty, so no conclusions could be drawn.[802]

» Most children with mild disease can be managed with supportive care alone.[19]

adjunct antipyretic/analgesic

Treatment recommended for SOME patients in selected patient group

Primary options

» acetaminophen: children: 10-15 mg/kg orally every 4-6 hours when required, maximum 75 mg/kg/day; adults: 325-1000 mg orally (immediate-release) every 4-6 hours when required, maximum 4000 mg/day

OR

» ibuprofen: children 6 months to 11 years of age: 5-10 mg/kg orally every 6-8 hours when required, maximum 40 mg/kg/day; children ≥12 years of age and adults: 200-400 mg orally every 4-6 hours when required, maximum 2400 mg/day

» Acetaminophen or ibuprofen are recommended.[87] [20]

» Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms. It is not recommended in pregnant women (especially in the third trimester) or children <6 months of age (age cut-offs vary by country).

adjunct monoclonal antibody

Treatment recommended for SOME patients in selected patient group
Manangement

**Acute**

**Primary options**

» **sotrovimab**: children ≥12 years of age and adults: consult specialist for guidance on dose

OR

» **casirivimab and imdevimab**: children ≥12 years of age and adults: consult specialist for guidance on dose

OR

» **bebtelovimab**: children ≥12 years of age and adults: consult specialist for guidance on dose

OR

» **bamlanivimab**: children and adults: consult specialist for guidance on dose (administered with etesevimab)

Consider a monoclonal antibody. Options may include sotrovimab, casirivimab/imdevimab, bamlanivimab/etesevimab, bebtelovimab, and regdanvimab, depending on your location. Guideline recommendations vary.

The World Health Organization recommends sotrovimab or casirivimab/imdevimab for patients with nonsevere disease who are at highest risk of hospitalization. Casirivimab/imdevimab should only be used where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e., excluding Omicron). Monoclonal antibodies probably reduce the risk of hospitalization and duration of symptoms in patients with nonsevere disease, based on moderate-certainty evidence. While monoclonal antibodies achieve a substantial reduction in the relative risk of hospitalization, the absolute benefit will be trivial or unimportant in absolute terms for all but those who are at highest risk of disease (e.g., unvaccinated, older people, immunodeficiencies, and/or chronic disease). Treatment is in addition to the current standard of care. The applicability of this recommendation to children is currently uncertain.  

[BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19](https://www.bmj.com/content/370/bmj.m3379)
In the UK, the National Institute for Health and Care Excellence recommends offering a neutralizing monoclonal antibody to patients ≥12 years of age who are not in hospital and are thought to be at high risk of progression to severe disease. Consult local guidance for monoclonal antibodies with current UK access.[20]

In the US, the National Institutes of Health guidelines panel recommends bebtelovimab for the treatment of nonhospitalized patients with mild to moderate disease who are at high risk of clinical progression. However, it is only recommended when preferred therapies (i.e., antivirals) are not available, feasible to use, or clinically appropriate as it has not been evaluated in patients at high risk of progression in placebo-controlled trials. Use may be considered in patients with mild to moderate disease who are hospitalized for a reason other than COVID-19 provided that they otherwise meet the criteria for outpatient treatment. The panel currently recommends against the use of casirivimab/imdevimab, bamlanivimab/etesevimab, and sotrovimab because Omicron is the dominant variant in the US, and these monoclonal antibodies are predicted to have markedly reduced susceptibility to Omicron and its subvariants.[19] These monoclonal antibodies are not currently authorized for use in the US.[803] [804]

The Infectious Diseases Society of America supports the use of monoclonal antibodies in ambulatory patients with mild to moderate disease who are at high risk for progression to severe disease, although it only recommends bebtelovimab in the context of a clinical trial.[510]

Choice of monoclonal antibody depends on availability, as well as clinical and contextual factors including emerging information about efficacy with different variants. Preclinical evidence has emerged suggesting that casirivimab/imdevimab and bamlanivimab/etesevimab lack neutralization activity against the Omicron variant in vitro. Sotrovimab and bebtelovimab appear to retain activity against Omicron; however, sotrovimab is not active against the Omicron BA.2 subvariant. Consult local guidance for details regarding specific variants and resistance. Logistical or supply constraints may make patient triage necessary. Treatment should be prioritized for patients who...
Acute

are at the highest risk of progressing to severe disease.[19] [20] [21]

» Evidence for the use of monoclonal antibodies in nonhospitalized patients is uncertain. A Cochrane review found that the evidence is insufficient to draw meaningful conclusions about any specific monoclonal antibody, and the disease stage in which it should be used. Information on outcomes in nonhospitalized patients such as mortality, quality of life, and serious adverse events is either inconclusive or entirely lacking, although casirivimab/imdevimab, sotrovimab, bamlanivimab (alone or in combination with etesevimab), and regdanvimab may reduce the occurrence of hospital admission or death (low-certainty evidence).[806]

» Monoclonal antibodies are administered by intravenous infusion. Casirivimab/imdevimab is also available in a subcutaneous formulation, but intravenous administration is recommended. However, if intravenous infusions are not feasible or would cause a delay in treatment, subcutaneous administration may be considered.[19] Evidence for subcutaneous administration is emerging.[805] Outpatient administration in specialized clinics is required, which may limit the feasibility of these treatments.[21] Administer as soon as possible after a positive test and within 7 days of symptom onset.[19] Dose varies across guidelines; consult local protocols.

» Hypersensitivity reactions, including infusion-related reactions and anaphylaxis, have been reported. Administer in a setting where severe hypersensitivity reactions can be managed. Monitor patients during the infusion and observe for at least 1 hour after infusion.

adjunct antiviral

Treatment recommended for SOME patients in selected patient group

Primary options

» remdesivir: children ≥12 years of age and ≥40 kg and adults: 200 mg intravenously as a loading dose on day 1, followed by 100 mg every 24 hours for 2 days

» Consider the antiviral agent remdesivir. Guideline recommendations vary.

» The World Health Organization conditionally recommends remdesivir for patients
Management

**Acute**

| ≥12 years of age (weighing ≥40 kg) with nonsevere disease who are at highest risk of hospitalization.[21] [795] [796] In the UK, the National Institute for Health and Care Excellence recommends remdesivir for patients ≥12 years of age (weighing ≥40 kg) who do not need supplemental oxygen, and are within 7 days of symptom onset, and are thought to be at high risk of progression to severe disease (based on low-certainty evidence). In the US, the National Institutes of Health guidelines panel recommends remdesivir to treat nonhospitalized patients with mild to moderate disease who are at high risk of clinical progression.[19] Remdesivir is approved in pediatric patients ≥28 days of age (weighing at least 7 lbs [3 kg]) in the US.[807] The Infectious Diseases Society of America supports the use of remdesivir in ambulatory patients with mild to moderate disease who are at high risk for progression to severe disease.[510]

- Remdesivir should be initiated as soon as possible, ideally within 7 days of symptom onset. The treatment course for this indication is 3 days. If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the healthcare provider’s discretion. Logistical constraints may make it difficult to administer the drug in some outpatient settings as it requires administration via intravenous infusion. Renal and/or hepatic monitoring may be required.[19] [20] [21]

- Adverse effects include nephrotoxicity and hepatotoxicity. Remdesivir is not recommended in patients with an estimated glomerular filtration rate <30 mL/minute. Monitor renal function before starting treatment and during treatment as clinically appropriate. Intravenous formulations contain the solubility enhancer sulfobutyl ether beta-cyclodextrin sodium (SBEDC), which is renally cleared. Accumulation of SBEDC in patients with renal impairment may result in liver and renal toxicities. Consider preferential use of the lyophilized powder formulation in patients with renal impairment if available, as it contains less SBEDC. Remdesivir may have little or no effect on acute kidney injury compared with placebo; however, the certainty of evidence is low.[906] Transaminase elevations have been reported. Monitor liver function before starting treatment and during treatment as clinically appropriate. Consider discontinuing treatment if alanine aminotransferase (ALT) levels increase to ≥10 times the upper limit of normal. Discontinue treatment if ALT elevation...
Acute

is accompanied by signs or symptoms of liver inflammation. Monitor prothrombin time before starting treatment and during treatment as clinically appropriate as increases in prothrombin time have been reported.

» Hypersensitivity reactions, including infusion-related reactions and anaphylaxis, have been reported. Administer in a setting where severe hypersensitivity reactions can be managed. Monitor patients during the infusion and observe for at least 1 hour after infusion.

» Evidence for this indication is emerging. Remdesivir probably reduces hospital admission (moderate-certainty evidence), and may have little or no impact on mortality (low-certainty evidence). The effect on mechanical ventilation and time to symptom resolution is very uncertain. The balance between benefits and potential harms favors treatment, but only in the highest risk group.[21] [795] [796] A randomized, double-blind, placebo-controlled trial of 562 patients found that a 3-day course of remdesivir resulted in an 87% lower risk of hospitalization or death among nonhospitalized patients who were at high risk for disease progression compared with placebo. The most common coexisting conditions were diabetes, obesity, and hypertension.[808]

» Logistical or supply constraints may make patient triage for antiviral treatment necessary. Therapy should be prioritized for patients who are at the highest risk of progressing to severe disease.

» Oral antiviral agents (e.g., molnupiravir, nirmatrelvir/ritonavir) are also available and may be recommended. The World Health Organization states that nirmatrelvir/ritonavir may represent a superior choice to remdesivir (and monoclonal antibodies).[21] [795] [796] See the Emerging section for more information on oral antiviral agents.

moderate COVID-19

1st consider home isolation or hospital admission

» Isolate patients with suspected or confirmed moderate disease (i.e., clinical signs of pneumonia but no signs of severe pneumonia) to contain virus transmission.[87]

» Manage patients in a healthcare facility, in a community facility, or at home. Home isolation,
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with telemedicine or remote visits as appropriate, can be considered in low-risk patients. Manage patients at high risk of deterioration and pregnant women in a healthcare facility.[87][19]

» Implement local infection prevention and control procedures when managing patients with COVID-19. For patients in home isolation, advise patients and household members to follow appropriate infection prevention and control measures:


» Guidance on when to stop isolation varies widely across locations. Isolation periods may depend on various factors including vaccination status, circulating SARS-CoV-2 variants, and patient factors (e.g., immunocompetent/immunocompromised, asymptomatic/symptomatic, disease severity). The World Health Organization recommends discontinuing transmission-based precautions (including isolation) and releasing patients from the care pathway 10 days after positive test (asymptomatic patients), or 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms (symptomatic patients).[87] However, some countries now recommend isolation periods as short as 5 days to 7 days.[797] Consult your local public health guidance for more information.

### plus monitoring

Treatment recommended for ALL patients in selected patient group

» Closely monitor patients for signs or symptoms of disease progression. If the patient is being managed at home, counsel them about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty...
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Acute breathing, chest pain).[87] [19] Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalized. Patient education and appropriate follow-up are required.[87] If the patient is being managed in hospital, monitor patients closely for signs of clinical deterioration using medical early warning scores (e.g., National Early Warning Score 2 [NEWS2]), and respond immediately with appropriate supportive care interventions.[87]

plus symptom management and supportive care

Treatment recommended for ALL patients in selected patient group

» Advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough.[20] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[800]

» Advise patients about adequate nutrition and appropriate rehydration. Advise patients to drink fluids regularly to avoid dehydration. Fluid intake needs can be higher than usual because of fever. However, too much fluid can worsen oxygenation.[87] [20]

» Advise patients to improve air circulation by opening a window or door.[20]

» Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[87]

» Consider treatment for olfactory dysfunction (e.g., olfactory training) if it persists beyond 2 weeks. There is no evidence to support the use of these treatments in patients with COVID-19.[801] A Cochrane review found there is very limited evidence regarding the efficacy of different interventions at preventing persistent olfactory dysfunction following infection. The only evidence available is for intranasal corticosteroids, and this is of very low certainty, so no conclusions could be drawn.[802]

» Most children with moderate disease can be managed with supportive care alone.[19]
Adjunct antibiotics
Treatment recommended for some patients in selected patient group

» Consider empiric antibiotics only if there is clinical suspicion of secondary bacterial infection. Start treatment as soon as possible, and refer to local guidelines for choice of regimen.[87] [19] [20] The regimen should be based on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.

» Antibiotics may also be considered in older people (particularly those in long-term care facilities) and children <5 years of age to provide empiric antibiotic treatment for possible pneumonia.[87]

» Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.[20]

» Advise patients to seek medical help without delay if their symptoms do not improve, or worsen rapidly or significantly. Reconsider whether the person has signs and symptoms of more severe disease on reassessment, and whether to refer them to hospital, other acute community support services, or palliative care services.[20]

Adjunct antipyretic/analgesic
Treatment recommended for some patients in selected patient group

Primary options

» acetaminophen: children: 10-15 mg/kg orally every 4-6 hours when required, maximum 75 mg/kg/day; adults: 325-1000 mg orally (immediate-release) every 4-6 hours when required, maximum 4000 mg/day

OR

» ibuprofen: children 6 months to 11 years of age: 5-10 mg/kg orally every 6-8 hours when required, maximum 40 mg/kg/day; children ≥12 years of age and adults: 200-400 mg orally every 4-6 hours when required, maximum 2400 mg/day

» Acetaminophen or ibuprofen are recommended.[87] [20]
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- Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms. It is not recommended in pregnant women (especially in the third trimester) or children <6 months of age (age cut-offs vary by country).

adjunct **monoclonal antibody**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **sotrovimab**: children ≥12 years of age and adults: consult specialist for guidance on dose

OR

- **casirivimab and imdevimab**: children ≥12 years of age and adults: consult specialist for guidance on dose

OR

- **bebtelovimab**: children ≥12 years of age and adults: consult specialist for guidance on dose

OR

- **bamlanivimab**: children and adults: consult specialist for guidance on dose (administered with etesevimab)

Consider a monoclonal antibody. Options may include sotrovimab, casirivimab/imdevimab, bamlanivimab/etesevimab, bebtelovimab, and regdanvimab, depending on your location. Guideline recommendations vary.

- The World Health Organization recommends sotrovimab or casirivimab/imdevimab for patients with nonsevere disease who are at highest risk of hospitalization. Casirivimab/imdevimab should only be used where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e., excluding Omicron). Monoclonal antibodies probably reduce the risk of hospitalization and duration of symptoms in patients with nonsevere disease, based on moderate-certainty evidence. While monoclonal antibodies achieve a substantial reduction in the relative risk of hospitalization, the absolute benefit will be trivial or unimportant in absolute terms for all but those who are at highest risk of disease (e.g., unvaccinated, older people, immunodeficiencies,
and/or chronic disease). Treatment is in addition to the current standard of care. The applicability of this recommendation to children is currently uncertain.[21] [795] [796]

» [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19] (https://www.bmj.com/content/370/bmj.m3379)

» In the UK, the National Institute for Health and Care Excellence recommends offering a neutralizing monoclonal antibody to patients ≥12 years of age who are not in hospital and are thought to be at high risk of progression to severe disease. Consult local guidance for monoclonal antibodies with current UK access.[20]

» In the US, the National Institutes of Health guidelines panel recommends bebtelovimab for the treatment of nonhospitalized patients with mild to moderate disease who are at high risk of clinical progression. However, it is only recommended when preferred therapies (i.e., antivirals) are not available, feasible to use, or clinically appropriate as it has not been evaluated in patients at high risk of progression in placebo-controlled trials. Use may be considered in patients with mild to moderate disease who are hospitalized for a reason other than COVID-19 provided that they otherwise meet the criteria for outpatient treatment. The panel currently recommends against the use of casirivimab/imdevimab, bamlanivimab/etesevimab, and sotrovimab because Omicron is the dominant variant in the US, and these monoclonal antibody combinations are predicted to have markedly reduced susceptibility to Omicron and its subvariants.[19] These monoclonal antibodies are not currently authorized for use in the US.[803] [804]

» The Infectious Diseases Society of America supports the use of monoclonal antibodies in ambulatory patients with mild to moderate disease who are at high risk for progression to severe disease, although it only recommends bebtelovimab in the context of a clinical trial.[510]

» Choice of monoclonal antibody depends on availability, as well as clinical and contextual factors including emerging information about efficacy with different variants. Preclinical evidence has emerged suggesting that casirivimab/imdevimab and bamlanivimab/etesevimab lack neutralization activity against...
the Omicron variant in vitro. Sotrovimab and bebtelovimab appear to retain activity against Omicron; however, sotrovimab is not active against the Omicron BA.2 subvariant. Consult local guidance for details regarding specific variants and resistance. Logistical or supply constraints may make patient triage necessary. Treatment should be prioritized for patients who are at the highest risk of progressing to severe disease.[19] [20] [21]

» Evidence for the use of monoclonal antibodies in nonhospitalized patients is uncertain. A Cochrane review found that the evidence is insufficient to draw meaningful conclusions about any specific monoclonal antibody, and the disease stage in which it should be used. Information on outcomes in nonhospitalized patients such as mortality, quality of life, and serious adverse events is either inconclusive or entirely lacking, although casirivimab/imdevimab, sotrovimab, bamlanivimab (alone or in combination with etesevimab), and regdanvimab may reduce the occurrence of hospital admission or death (low-certainty evidence).[806]

» Monoclonal antibodies are administered by intravenous infusion. Casirivimab/imdevimab is also available in a subcutaneous formulation, but intravenous administration is recommended. However, if intravenous infusions are not feasible or would cause a delay in treatment, subcutaneous administration may be considered.[19] Evidence for subcutaneous administration is emerging.[805] Outpatient administration in specialized clinics is required, which may limit the feasibility of these treatments.[21] Administer as soon as possible after a positive test and within 7 days of symptom onset. Dose varies across guidelines; consult local protocols.

» Hypersensitivity reactions, including infusion-related reactions and anaphylaxis, have been reported. Administer in a setting where severe hypersensitivity reactions can be managed. Monitor patients during the infusion and observe for at least 1 hour after infusion.

**adjunct antiviral**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» remdesivir: children ≥12 years of age and ≥40 kg and adults: 200 mg intravenously as
### Acute

- a loading dose on day 1, followed by 100 mg every 24 hours for 2 days

- Consider the antiviral agent remdesivir. Guideline recommendations vary.

- The World Health Organization conditionally recommends remdesivir for patients ≥12 years of age (weighing ≥40 kg) with nonsevere disease who are at highest risk of hospitalization. In the UK, the National Institute for Health and Care Excellence recommends remdesivir for patients ≥12 years of age (weighing ≥40 kg) who do not need supplemental oxygen, and are within 7 days of symptom onset, and are thought to be at high risk of progression to severe disease (based on low-certainty evidence). In the US, the National Institutes of Health guidelines panel recommends remdesivir to treat nonhospitalized patients with mild to moderate disease who are at high risk of clinical progression. Remdesivir is approved in pediatric patients ≥28 days of age (weighing at least 7 lbs [3 kg]) in the US. The Infectious Diseases Society of America supports the use of remdesivir in ambulatory patients with mild to moderate disease who are at high risk for progression to severe disease.

- Remdesivir should be initiated as soon as possible, ideally within 7 days of symptom onset. The treatment course for this indication is 3 days. Logistical constraints may make it difficult to administer the drug in some outpatient settings as it requires administration via intravenous infusion. Renal and/or hepatic monitoring may be required.

- Adverse effects include nephrotoxicity and hepatotoxicity. Remdesivir is not recommended in patients with an estimated glomerular filtration rate <30 mL/minute. Monitor renal function before starting treatment and during treatment as clinically appropriate. Intravenous formulations contain the solubility enhancer sulfobutyl ether beta-cyclodextrin sodium (SBECD), which is renally cleared. Accumulation of SBECD in patients with renal impairment may result in liver and renal toxicities. Consider preferential use of the lyophilized powder formulation in patients with renal impairment if available, as it contains less SBECD. Remdesivir may have little or no effect on acute kidney injury compared with placebo; however, the certainty of evidence is low. Transaminase elevations have been reported. Monitor liver function before starting treatment and during treatment as necessary.
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<table>
<thead>
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<th>1st hospital admission</th>
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<tr>
<td>Admit patients with suspected or confirmed severe disease to an appropriate healthcare facility under the guidance of a specialist team</td>
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clinically appropriate. Consider discontinuing treatment if alanine aminotransferase (ALT) levels increase to ≥10 times the upper limit of normal. Discontinue treatment if ALT elevation is accompanied by signs or symptoms of liver inflammation. Monitor prothrombin time before starting treatment and during treatment as clinically appropriate as increases in prothrombin time have been reported.

- Hypersensitivity reactions, including infusion-related reactions and anaphylaxis, have been reported. Administer in a setting where severe hypersensitivity reactions can be managed. Monitor patients during the infusion and observe for at least 1 hour after infusion.

- Evidence for this indication is emerging. Remdesivir probably reduces hospital admission (moderate-certainty evidence), and may have little or no impact on mortality (low-certainty evidence). The effect on mechanical ventilation and time to symptom resolution is very uncertain. The balance between benefits and potential harms favors treatment, but only in the highest risk group.[21] [795] [796] A randomized, double-blind, placebo-controlled trial of 562 patients found that a 3-day course of remdesivir resulted in an 87% lower risk of hospitalization or death among nonhospitalized patients who were at high risk for disease progression compared with placebo. The most common coexisting conditions were diabetes, obesity, and hypertension.[808]

- Logistical or supply constraints may make patient triage for antiviral treatment necessary. Therapy should be prioritized for patients who are at the highest risk of progressing to severe disease.

- Oral antiviral agents (e.g., molnupiravir, nirmatrelvir/ritonavir) are also available and may be recommended. The World Health Organization states that nirmatrelvir/ritonavir may represent a superior choice to remdesivir (and monoclonal antibodies).[21] [795] [796] See the Emerging section for more information on oral antiviral agents.
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as these patients are at risk of rapid clinical deterioration.

» Severe disease in adults is defined as having clinical signs of pneumonia plus at least one of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or SpO₂ <90% on room air. Severe disease in children is defined as having clinical signs of pneumonia plus at least one of the following: central cyanosis or SpO₂ <90%, severe respiratory distress, general danger signs (inability to breastfeed or drink, lethargy or unconsciousness, or convulsions), or fast breathing (<2 months: ≥60 breaths per minute; 2-11 months: ≥50 breaths per minute; 1-5 years: ≥40 breaths per minute).[87]

» Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as midwifery and mental health and psychosocial support. A woman-centered, respectful, skilled approach to care is recommended.[87] The multidisciplinary team should be organized as soon as possible after maternal hypoxemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.[895]

» Implement local infection prevention and control procedures when managing patients with COVID-19.

» Use the Clinical Frailty Scale (CFS) to assess baseline health and inform discussions on treatment expectations when appropriate and within an individualized assessment of frailty. [Clinical Frailty Scale] (https://www.scfn.org.uk/clinical-frailty-scale) Do not use the CFS for younger people, people with stable long-term disabilities (e.g., cerebral palsy), learning disabilities, or autism. Make an individualized assessment of frailty in these people, using clinical assessment and alternative scoring methods.[20] Hospitalized frail patients are at higher risk of all-cause mortality compared with non-frail hospitalized patients, regardless of the frailty score/assessment tool used.[810] A meta-analysis found that an increase in CFS was associated with an increase in mortality (each 1-point increase in CFS was associated with a 12% increase in mortality).[811] Patients with a score between 4-9 had significantly increased mortality compared with those with a score of 1-3.[812] However, one systematic review and meta-analysis found that there was no difference in short-term mortality between frail and nonfrail
Acute patients. Some studies suggest that a more nuanced understanding of frailty and outcomes is needed, and you should exercise caution in placing too much emphasis on the influence of frailty alone when discussing prognosis in older people.

» Guidance on when to stop isolation varies widely across locations. Isolation periods may depend on various factors including vaccination status, circulating SARS-CoV-2 variants, and patient factors (e.g., immunocompetent/ immunocompromised, asymptomatic/ symptomatic, disease severity). The World Health Organization recommends discontinuing transmission-based precautions (including isolation) and releasing patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms. However, this guidance varies and you should consult your local public health guidance for more information.

plus **consider oxygen therapy**

Treatment recommended for ALL patients in selected patient group

» Start supplemental oxygen therapy immediately in any patient with emergency signs (i.e., obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions), or any patient without emergency signs and \( \text{SpO}_2 < 90\% \).

» Target \( \text{SpO}_2 \) to \( \geq 94\% \) during resuscitation in adults and children with emergency signs who require emergency airway management and oxygen therapy. Once the patient is stable, a target \( \text{SpO}_2 > 90\% \) in children and nonpregnant adults, and \( \geq 92\% \) to 95\% in pregnant women, is recommended. Nasal prongs or a nasal cannula are preferred in young children. Some guidelines recommend that \( \text{SpO}_2 \) should be maintained no higher than 96\%.

» Some centers may recommend different \( \text{SpO}_2 \) targets in order to support prioritization of oxygen flow for the most severely ill patients in hospital.

» Consider positioning techniques (e.g., high supported sitting), and airway clearance management to optimize oxygenation and assist with secretion clearance in adults. Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require supplemental oxygen. \( \text{SpO}_2 \) to \( \geq 92\% \) to 95\% in pregnant women, is recommended. Nasal prongs or a nasal cannula are preferred in young children. Some guidelines recommend that \( \text{SpO}_2 \) should be maintained no higher than 96\%.

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nonintubated patients was associated with improvement in oxygen variables (PaO₂/FiO₂, PaO₂, and SpO₂), respiratory rate, rate of intubation, and mortality. However, evidence is limited.[817] [818] [819] [820] However, one small nonrandomized controlled trial found that prone positioning offered no clinical benefit among patients with hypoxemia who are not on mechanical ventilation, with evidence of worsening clinical outcomes at day 5.[821]

» Monitor patients closely for signs of progressive acute hypoxemic respiratory failure.[87] [19]

plus symptom management and supportive care

Treatment recommended for ALL patients in selected patient group

» Fluids and electrolytes: use cautious fluid management in adults and children without tissue hypoperfusion and fluid responsiveness as aggressive fluid resuscitation may worsen oxygenation.[87] Correct any electrolyte or metabolic abnormalities, such as hyperglycemia or metabolic acidosis, according to local protocols.[822]

» Cough: advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough. Short-term use of a cough suppressant may be considered in select patients (e.g., if the cough is distressing to the patient) provided there are no contraindications.[20] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[800]

» Breathlessness: keep the room cool, and encourage relaxation, breathing techniques, and changing body positions. Identify and treat any reversible causes of breathlessness (e.g., pulmonary edema, pulmonary embolism, COPD, asthma). Consider a trial of oxygen, if available.[20]

» Anxiety, delirium, and agitation: identify and treat any underlying or reversible causes (e.g., offer reassurance, treat hypoxia, correct metabolic or endocrine abnormalities, address coinfections, minimize use of drugs that may cause or worsen delirium, treat substance withdrawal, maintain normal sleep cycles, treat pain or breathlessness).[87]
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[20] Low doses of haloperidol (or another suitable antipsychotic) can be considered for agitation.[87] Nonpharmacologic interventions are the mainstay for the management of delirium when possible, and prevention is key.[823]

» Mouth care: an important part of overall patient care in hospitalized patients who are ventilated or nonventilated and those undergoing step-down or end-of-life care.[824]

» Mental health symptoms: provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia or depression as appropriate.[87]

plus venous thromboembolism prophylaxis

Treatment recommended for ALL patients in selected patient group

Primary options

» enoxaparin: consult specialist for guidance on dose

OR

» dalteparin: consult specialist for guidance on dose

Secondary options

» fondaparinux: consult specialist for guidance on dose

OR

» heparin: consult specialist for guidance on dose

» Assess the risk of bleeding as soon as possible after admission, or by the time of the first consultant review, using a suitable risk assessment tool.[20]

» Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalized adults and adolescents, provided there are no contraindications.[87] [19] [825] [826] In the UK, the National Institute for Health and Care Excellence (NICE) recommends starting as soon as possible (within 14 hours of admission), in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk, and continuing for a minimum of 7 days including after discharge.[20] In children, the indications for venous thromboembolism...
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Acute prophylaxis should be the same as those for children without COVID-19.[19]

» Low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options for standard thromboprophylaxis.[87] In the UK, NICE recommends low molecular weight heparin first-line, with fondaparinux or unfractionated heparin reserved for patients who cannot have low molecular weight heparin.[20] In the US, the National Institutes of Health guidelines panel recommends parenteral over oral anticoagulants and, when heparin is used, low molecular weight heparin is preferred over unfractionated heparin. The panel recommends against the use of therapeutic-dose oral anticoagulants, except in the context of a clinical trial.[19] Unfractionated heparin is contraindicated in patients with severe thrombocytopenia and patients with a history of heparin-induced thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia. Mechanical thromboprophylaxis (e.g., intermittent pneumatic compression devices) is recommended if anticoagulation is contraindicated or not available.[826] [827]

» The optimal dose is yet to be determined. Standard prophylaxis doses are generally recommended over intermediate- or full treatment-dose regimens in patients without an established indication for higher-dose anticoagulation across most guidelines.[830] However, this recommendation varies and you should consult your local guidelines. The World Health Organization recommends standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing in patients without an established indication for higher-dose anticoagulation.[87] In the UK, NICE recommends a prophylactic dose of a low molecular weight heparin for a minimum of 7 days (including after discharge) in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk. A treatment dose of a low molecular weight heparin for 14 days or until discharge (whichever is sooner) may be considered in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk; however, this is a conditional recommendation only. The decision should be carefully considered, and choice of the most appropriate dose regimen should be guided by bleeding risk, clinical judgment, and local protocols. For those who do not need supplemental oxygen, follow...
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standard VTE prophylaxis guidelines.[20] In the US, the National Institutes of Health guidelines panel recommends prophylactic-dose heparin (low molecular weight heparin preferred over unfractionated heparin) for patients who are hospitalized but do not require supplemental oxygen, and therapeutic-dose heparin for patients who have a D-dimer level above the upper limit of normal, require low-flow oxygen, and have no increased bleeding risk. Treatment should continue for 14 days or until hospital discharge, whichever comes first. The panel recommends using prophylactic-dose heparin for patients who are not administered therapeutic heparin, unless a contraindication exists.[19] Dose adjustments may be required in patients with extremes of body weight or renal impairment.[20]

» For patients who are already on an anticoagulant for another underlying condition, continue the patient’s current medication and therapeutic dose unless contraindicated by a change in clinical circumstances.[19] [20] Consider switching to low molecular weight heparin as the preferred option for venous thromboembolism prophylaxis if the patient’s clinical condition is deteriorating and the patient is not currently on low molecular weight heparin.[20]

» Evidence supports the use of lower-dose anticoagulant regimens. A Cochrane review found that higher-dose regimens resulted in little to no difference in all-cause mortality compared with lower-dose regimens in hospitalized patients; however, higher-dose regimens were associated with an increased risk of minor bleeding up to 30 days (high-certainty evidence). Higher-dose anticoagulants probably reduce pulmonary embolism and slightly increase major bleeding compared with lower-dose regimens up to 30 days (moderate-certainty evidence). Higher-dose anticoagulants may result in little or no difference in deep vein thrombosis, stroke, major adverse limb events, myocardial infarction, atrial fibrillation, or thrombocytopenia compared with lower-dose regimens up to 30 days (low-certainty evidence). Anticoagulants may reduce all-cause mortality compared with no anticoagulants, but the evidence is very uncertain.[831]

» Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected.[87] If the
patient’s clinical condition changes, assess the risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.[20]

» Continue until hospital discharge.[87] Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients.[19] [825] [826] Ensure patients who require VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.[20]

» There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulation in hospitalized patients with COVID-19.[836] A systematic review and meta-analysis found that the pooled odds of mortality between anticoagulated and nonanticoagulated hospitalized patients were similar, but lower in the standard prophylactic-dose group. Prophylactic-dose anticoagulation significantly decreased the odds of in-hospital death by 17% compared with no anticoagulation. Mortality increased in the intermediate- to therapeutic-dose group with an increased risk of major bleeding.[837]Clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[825]

### plus monitoring
Treatment recommended for ALL patients in selected patient group

» Monitor patients closely for signs of clinical deterioration, and respond immediately with appropriate supportive care interventions.[87]

### adjunct antibiotics
Treatment recommended for SOME patients in selected patient group

» Consider empiric antibiotics if there is clinical suspicion of secondary bacterial infection. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria (or within 4 hours of establishing a diagnosis of secondary bacterial pneumonia); do not wait for microbiology results. Base the regimen on the clinical diagnosis (e.g., community-acquired pneumonia, hospital-acquired pneumonia, sepsis), local epidemiology and susceptibility data, and local treatment guidelines.[87] [19] [20]

» Do not offer antibiotics for preventing or treating pneumonia if SARS-CoV-2, another
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- There is insufficient evidence to recommend empiric broad-spectrum antibiotics in the absence of another indication.\(^{[19]}\)

- Consider seeking specialist advice for people who: are immunocompromised; have a history of infection with resistant organisms; have a history of repeated infective exacerbations of lung disease; are pregnant; or are receiving advanced respiratory or organ support.\(^{[20]}\) Seek specialist advice if there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic, or there is clinical or microbiologic evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.\(^{[20]}\)

- Reassess antibiotic use daily. De-escalate empiric therapy on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching from intravenous to oral therapy. Duration of treatment should be as short as possible (e.g., 5 to 7 days). Antibiotic stewardship programs should be in place.\(^{[87]}\)

### Adjunct corticosteroid

- Treatment recommended for SOME patients in selected patient group

#### Primary options

- **dexamethasone**: children: consult specialist for guidance on dose; adults: 6 mg orally/intravenously once daily for 7-10 days

- **hydrocortisone**: children: consult specialist for guidance on dose; adults: 50 mg orally/intravenously every 8 hours for 7-10 days

#### Secondary options

- **prednisone**: children: consult specialist for guidance on dose; adults: 40 mg/day orally given in 1-2 divided doses for 7-10 days

- **methylprednisolone**: children: consult specialist for guidance on dose; adults: 32 mg/day orally/intravenously given in 1-2 divided doses for 7-10 days

- Consider a systemic corticosteroid. Guideline recommendations vary.
The World Health Organization strongly recommends systemic corticosteroid therapy (low-dose intravenous or oral dexamethasone or hydrocortisone) for 7 to 10 days in adults with severe disease. This recommendation is based on two meta-analyses that pooled data from eight randomized trials (over 7000 patients), including the UK RECOVERY trial. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe disease. There is no evidence directly comparing dexamethasone and hydrocortisone. The harms of treatment in this context are considered to be minor. It is unclear whether these recommendations can be applied to children or those who are immunocompromised.

In the UK, the National Institute for Health and Care Excellence recommends offering dexamethasone (or an alternative such as hydrocortisone or prednisone when dexamethasone cannot be used or is unavailable) to people who need supplemental oxygen to meet their prescribed oxygen saturation levels, or who have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. Treatment is for up to 10 days unless there is a clear indication to stop early.

In the US, the National Institutes of Health guidelines panel recommends dexamethasone, either alone or in combination with remdesivir, in hospitalized adults who require supplemental oxygen. Alternative corticosteroids may be used in situations where dexamethasone is not available. It is not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., via a nasal cannula only). Use of dexamethasone for the treatment of severe disease in children who are profoundly immunocompromised has not been evaluated, may be harmful, and therefore should be considered only on a case-by-case basis.

Moderate- and low-certainty evidence supports the use of corticosteroids in hospitalized patients. A Cochrane review found that systemic corticosteroids probably slightly reduce all-
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cause mortality in hospitalized patients with symptomatic disease. Most participants in the studies were treated with noninvasive or invasive mechanical ventilation. Low-certainty evidence suggests that there may also be a reduction in ventilator-free days; however, the current evidence remains uncertain due to methodological limitations. Evidence of an increased risk of mortality in symptomatic hospitalized patients without any need for additional oxygen was limited by a lack of statistical significance. It is unknown which systemic corticosteroid is most effective.\[841\]

» Monitor patients for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.\[19\]

adjunct antiviral

Treatment recommended for SOME patients in selected patient group

Primary options

» remdesivir: children ≥12 years of age and ≥40 kg and adults: 200 mg intravenously as a loading dose on day 1, followed by 100 mg every 24 hours for 5-10 days

» Consider the antiviral agent remdesivir. Guideline recommendations vary, and there are conflicting recommendations across international guidelines.

» In the UK, the National Institute for Health and Care Excellence recommends considering remdesivir in hospitalized adults and children ≥12 years of age (weighing ≥40 kg) who require low-flow supplemental oxygen. Limited evidence suggests that remdesivir probably reduces the risk of death in hospitalized patients who need low-flow supplemental oxygen (moderate certainty). This is likely because it is being given early in the disease course.\[20\]

» In the US, the National Institutes of Health guidelines panel recommends remdesivir in hospitalized adults who require supplemental oxygen. It may be given alone (e.g., for patients who require minimal supplemental oxygen) or in combination with dexamethasone (e.g., for patients who require increasing amounts of supplemental oxygen). The panel recommends remdesivir in hospitalized children ages ≥12 years who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen. The panel recommends
remdesivir in hospitalized children ages ≥16 years who have an emergent or increasing need for supplemental oxygen, regardless of whether they have risk factors for severe disease. The panel recommends considering remdesivir in hospitalized children of all ages who have an emergent or increasing need for supplemental oxygen, in consultation with a pediatric infectious disease specialist.[19] Remdesivir is approved in pediatric patients ≥28 days of age (weighing at least 7 lbs [3 kg]) in the US.[807]

» The Infectious Diseases Society of America supports the use of remdesivir in hospitalized patients with severe disease who require oxygen.[510]

» The World Health Organization recommends against the use of remdesivir in hospitalized patients in addition to standard care, regardless of disease severity. This weak or conditional recommendation is based on a systematic review and network meta-analysis of four randomized trials with 7333 hospitalized patients, and included the ACTT-1 trial and preliminary results from the WHO Solidarity trial. At the time of publication, there was no evidence that remdesivir improved patient outcomes such as time to clinical improvement, the need for mechanical ventilation, or mortality. However, the meta-analysis did not prove that remdesivir had no benefit. Updated results from the WHO Solidarity trial published in May 2022 found that remdesivir may have a small effect against death and/or progression to ventilation. Overall, 14.5% of patients receiving remdesivir died compared with 15.6% in the control group. However, remdesivir had no significant effect on patients who were already being ventilated. In patients who were already ventilated, 42.1% of patients receiving remdesivir died compared with 38.5% in the control group. In patients who were not already ventilated, 11.9% of patients receiving remdesivir died compared with 13.5% in the control group, while 14.1% versus 15.7% progressed to ventilation.[843] This recommendation is currently being reviewed, with an updated recommendation expected soon.[21] [795] [796] [842]

» Moderate-certainty evidence does not support the use of remdesivir in hospitalized patients. A Cochrane review found that remdesivir probably has little or no effect on 28-day all-cause mortality in hospitalized patients compared with placebo or usual care (moderate certainty). Effects on clinical improvement or worsening
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were uncertain. There were insufficient data available to examine the effect of remdesivir on mortality across subgroups defined by respiratory support at baseline.[844]

» The recommended treatment course for this indication is 5 days or until hospital discharge, whichever comes first.[19] Evidence does not suggest any greater benefit with a 10-day course of remdesivir compared with a 5-day course, but suggests an increased risk of harm.[20] However, some experts may recommend a 10-day course in patients who have not shown substantial clinical improvement by day 5.[19] There may be no benefit in completing the full course of remdesivir if the patient progresses.[20] However, US guidelines recommend completing the full treatment course if the patient progresses to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation.[19]

» Adverse effects include nephrotoxicity and hepatotoxicity. Remdesivir is not recommended in patients with an estimated glomerular filtration rate <30 mL/minute. Monitor renal function before starting treatment and during treatment as clinically appropriate. Intravenous formulations contain the solubility enhancer sulfobutyl ether beta-cyclodextrin sodium (SBECD), which is renally cleared. Accumulation of SBECD in patients with renal impairment may result in liver and renal toxicities. Consider preferential use of the lyophilized powder formulation in patients with renal impairment if available, as it contains less SBECD. Remdesivir may have little or no effect on acute kidney injury compared with placebo; however, the certainty of evidence is low.[906] Transaminase elevations have been reported. Monitor liver function before starting treatment and during treatment as clinically appropriate. Consider discontinuing treatment if alanine aminotransferase (ALT) levels increase to ≥10 times the upper limit of normal. Discontinue treatment if ALT elevation is accompanied by signs or symptoms of liver inflammation. Monitor prothrombin time before starting treatment and during treatment as clinically appropriate as increases in prothrombin time have been reported.

» Hypersensitivity reactions, including infusion-related reactions and anaphylaxis, have been reported. Administer in a setting where severe hypersensitivity reactions can be managed.
Monitor patients during the infusion and observe for at least 1 hour after infusion.

**adjunct interleukin-6 (IL-6) inhibitor**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **tocilizumab**: children: consult specialist for guidance on dose; adults: 8 mg/kg intravenously as a single dose, maximum 800 mg/dose
  Typically administered as a single intravenous dose; however, a second dose may be administered 12 to 48 hours after the first dose if the clinical response is inadequate.

- **sarilumab**: children: consult specialist for guidance on dose; adults: 400 mg intravenously as a single dose
  Typically administered as a single intravenous dose; however, a second dose may be administered 12 to 48 hours after the first dose if the clinical response is inadequate.

- Consider an IL-6 inhibitor. Guideline recommendations vary.

- The World Health Organization strongly recommends an IL-6 inhibitor (tocilizumab or sarilumab), in combination with a systemic corticosteroid and initiated at the same time, in patients with severe disease. This recommendation is based on high-certainty evidence that shows IL-6 inhibitors reduce mortality and the need for mechanical ventilation, and low-certainty evidence that suggests that IL-6 inhibitors may also reduce the duration of mechanical ventilation and hospitalization. The evidence regarding the risk of severe adverse events is uncertain. The applicability of this recommendation to children is currently uncertain.[21] [795] [796] This recommendation is based on data from the UK RECOVERY and REMAP-CAP trials.[845] [846]
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» [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19](https://www.bmj.com/content/370/bmj.m3379)

» In the UK, the National Institute for Health and Care Excellence recommends a single dose of tocilizumab in hospitalized adults if all of the following conditions apply: they are having or have completed a course of corticosteroids such as dexamethasone (unless they cannot have corticosteroids); they have not had another IL-6 inhibitor during this admission; there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab; AND they either need supplemental oxygen and have a C-reactive protein level of ≥75 mg/L, OR they are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, noninvasive ventilation, or invasive mechanical ventilation. Consider tocilizumab for children and young people who have severe disease or pediatric inflammatory multisystem syndrome only if they are ages 1 year and over, and only in the context of a clinical trial. Sarilumab may be considered an alternative option in adults only if tocilizumab cannot be used or is unavailable (use the same eligibility criteria as those for tocilizumab).[20]

» In the US, the National Institutes of Health guidelines panel recommends tocilizumab (or sarilumab if tocilizumab is not available or not feasible to use) for patients on a corticosteroid with rapidly increasing oxygen needs and systemic inflammation.[19] The Infectious Diseases Society of America recommends considering tocilizumab in hospitalized adults with progressive severe disease who have elevated markers of systemic inflammation, in addition to standard of care (i.e., corticosteroids), rather than standard of care alone. Sarilumab may be used if tocilizumab is not available.[510]

» IL-6 inhibitors and Janus kinase inhibitors (see table below) are viewed as alternatives to each other and should not be administered together. There is potential for an additive risk of infection.

» Patients on IL-6 inhibitors are at increased risk of infection including active tuberculosis, invasive fungal infections, and opportunistic pathogens.

» Routine blood work including neutrophil count, platelets, transaminases, and total bilirubin should be checked prior to initiation of therapy. All patients should be monitored for signs and symptoms of infection given the increased risk
**Acute**

<table>
<thead>
<tr>
<th>Janus kinase (JAK) inhibitor</th>
<th>Treatment recommended for SOME patients in selected patient group</th>
</tr>
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</table>

**Primary options**

- **baricitinib**: children: consult specialist for guidance on dose; adults: 4 mg orally once daily for 14 days

**Secondary options**

- **tofacitinib**: children and adults: consult specialist for guidance on dose

OR

- **ruxolitinib**: children and adults: consult specialist for guidance on dose

**Consider a JAK inhibitor. Guideline recommendations vary.**

- The World Health Organization strongly recommends a JAK inhibitor (baricitinib), in combination with a systemic corticosteroid and initiated at the same time, in patients with severe disease. This recommendation is based on moderate-certainty evidence that baricitinib probably reduces mortality and duration of mechanical ventilation, and high-certainty evidence that baricitinib reduces length of hospital stay. The applicability of this recommendation to children is currently uncertain.[21] [795] [796]

- [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19] (https://www.bmj.com/content/370/bmj.m3379)

- In the UK, the National Institute for Health and Care Excellence recommends baricitinib in hospitalized adults who: need supplemental oxygen, and are having or have completed a course of corticosteroids (unless contraindicated), and have no evidence of infection (other than SARS-CoV-2) that might be worsened by baricitinib. Baricitinib may also be considered in children ≥2 years of age provided they meet the same criteria.[20]
» In the US, the National Institutes of Health guidelines panel recommends baricitinib in patients on a corticosteroid with rapidly increasing oxygen needs and systemic inflammation.[19] The Infectious Diseases Society of America suggests baricitinib (in combination with a corticosteroid) in hospitalized adults with severe disease. It suggests baricitinib with remdesivir, rather than remdesivir alone, in patients who cannot receive a corticosteroid because of a contraindication.[510]

» Other drugs in this class include tofacitinib and ruxolitinib. The World Health Organization recommends against using these drugs unless baricitinib or IL-6 inhibitors are not available. The effects of tofacitinib or ruxolitinib on mortality, need for mechanical ventilation, and hospital length of stay remain uncertain and more trial evidence is needed.[21] [795] [796] In the US, the National Institutes of Health guidelines panel recommends tofacitinib only if baricitinib is not available or it is not feasible to use it.[19] The Infectious Diseases Society of America suggests tofacitinib in hospitalized adults with severe disease who are not on noninvasive or invasive mechanical ventilation.[510]

» JAK inhibitors and IL-6 inhibitors (see table above) are viewed as alternatives to each other and should not be administered together. There is potential for an additive risk of infection.

» Patients are at increased risk of infection including active tuberculosis, invasive fungal infections, and opportunistic pathogens.[21] Avoid use in patients with known active tuberculosis. All patients should be monitored for signs and symptoms of infection given the increased risk of immunosuppression in addition to systemic corticosteroids. Monitor complete blood count with differential before and during treatment.

» Baricitinib is not recommended in patients with severe renal or hepatic impairment.[21] Baricitinib is not recommended in adults with an estimated glomerular filtration rate ≤15 mL/minute (≤30 mL/minute in children <9 years of age), or in patients on dialysis or renal replacement therapy. A dose reduction is recommended in patients with an estimated glomerular filtration rate ≤60 mL/minute. Baricitinib has not been studied in patients with severe hepatic impairment and it is unknown whether a dose adjustment is required in these patients. It should only be used if the potential benefits outweigh the potential risks. Use caution
Acute

with tofacitinib and ruxolitinib in patients with moderate to severe renal impairment (including those on dialysis); a dose adjustment may be required. Monitor renal and hepatic function before and during treatment.

- Adverse effects include leukopenia, lymphopenia, thrombocytosis, anemia, blood clotting abnormalities, hepatic impairment, and secondary infection.[21] Other serious adverse effects include venous thrombosis and severe infections. The US Food and Drug Administration has issued a warning about increased risk of serious heart-related events, cancer, blood clots, and death with JAK inhibitors.[807]

adjunct treatment of coinfections

Treatment recommended for SOME patients in selected patient group

- Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.[87] The treatment of influenza is the same in all patients regardless of SARS-CoV-2 co-infection. Start empiric treatment with oseltamivir in hospitalized patients who are suspected of having either or both infections as soon as possible without waiting for influenza test results. Antiviral therapy can be stopped once influenza has been ruled out.[19]

adjunct antipyretic/analgesic

Treatment recommended for SOME patients in selected patient group

Primary options

- Acetaminophen: children: 10-15 mg/kg orally every 4-6 hours when required, maximum 75 mg/kg/day; adults: 325-1000 mg orally (immediate-release) every 4-6 hours when required, maximum 4000 mg/day

OR

- Ibuprofen: children 6 months to 11 years of age: 5-10 mg/kg orally every 6-8 hours when required, maximum 40 mg/kg/day; children ≥12 years of age and adults: 200-400 mg orally every 4-6 hours when required, maximum 2400 mg/day

- Acetaminophen or ibuprofen are recommended.[87] [20]

- Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms. It is not recommended
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in pregnant women (especially in the third trimester) or children <6 months of age (age cut-offs vary by country).

adjunct monoclonal antibody

Treatment recommended for SOME patients in selected patient group

Primary options

» sotrovimab: children ≥12 years of age and adults: consult specialist for guidance on dose

Secondary options

» casirivimab and imdevimab: children ≥12 years of age and adults: consult specialist for guidance on dose

OR

» bamlanivimab: children and adults: consult specialist for guidance on dose (administered with etesevimab)

Consider a monoclonal antibody. Options may include sotrovimab, casirivimab/imdevimab, and bamlanivimab/etesevimab, depending on your location. Guideline recommendations vary.

» The World Health Organization recommends casirivimab/imdevimab (but not sotrovimab) for patients with severe disease with a seronegative status (i.e., no detectable SARS-CoV-2 antibodies). Casirivimab/imdevimab should only be used where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e., excluding Omicron). Casirivimab/imdevimab probably reduces mortality and possibly reduces the need for mechanical ventilation in patients who are seronegative based on moderate- and low-certainty evidence, respectively. Sotrovimab did not demonstrate efficacy in seronegative patients with severe/critical disease in one randomized controlled trial. Treatment is in addition to the current standard of care. The applicability of this recommendation to children is currently uncertain.[21] [795] [796]

» [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19] (https://www.bmj.com/content/370/bmj.m3379)

» In the UK, the National Institute for Health and Care Excellence recommends casirivimab/imdevimab in hospitalized patients ≥12 years of age who are seronegative, provided they...
Acute

meet all of the eligibility criteria and none of the exclusion criteria (see guidance for more information).[20] Do not offer casirivimab/imdevimab to patients who are known or suspected to have infection caused by an Omicron variant. Only offer casirivimab/imdevimab to patients when the infection is known to be caused by a variant susceptible to casirivimab/imdevimab. A UK clinical commissioning policy also recommends sotrovimab for hospital-onset infection in certain patients (see guidance for more information).[853]

» In the US, the National Institutes of Health guidelines panel states that casirivimab/imdevimab and sotrovimab and bamlanivimab/etesevimab are not currently authorized for use in hospitalized patients with severe disease, but they may be available through expanded access programs for patients who are hospitalized with severe disease who have not developed an antibody response or who are not expected to mount an effective immune response (e.g., immunocompromised patients).[19]

» Choice of monoclonal antibody depends on availability, as well as clinical and contextual factors including emerging information about efficacy with different variants. Preclinical evidence has emerged suggesting that casirivimab/imdevimab and bamlanivimab/etesevimab lack neutralization activity against the Omicron variant in vitro. Sotrovimab appears to retain activity against Omicron; however, sotrovimab is not active against the Omicron BA.2 subvariant. Consult local guidance for details regarding specific variants and resistance. Logistical or supply constraints may make patient triage necessary. Treatment should be prioritized for patients who are at the highest risk of progressing to severe disease.[19][20][21]

» Evidence for the use of monoclonal antibodies in hospitalized patients is uncertain. A Cochrane review found that casirivimab/imdevimab probably has no effect on mortality, progression to invasive mechanical ventilation, and 30-day hospital discharge in hospitalized patients (moderate-certainty evidence). Bamlanivimab may have little to no effect on efficacy outcomes when compared with placebo, but it may increase the occurrence of severe symptoms and adverse events (low-certainty evidence).[806] The UK RECOVERY trial found that casirivimab/imdevimab reduced 28-day
### Acute

- Mortality in hospitalized patients who were seronegative at baseline, but not in those who were seropositive at baseline.[854]

  » Monoclonal antibodies are administered by intravenous infusion. Casirivimab/imdevimab is also available in a subcutaneous formulation, but intravenous administration is recommended. However, if intravenous infusions are not feasible or would cause a delay in treatment, subcutaneous administration may be considered.[19] Dose varies across guidelines; consult local protocols.

  » Hypersensitivity reactions, including infusion-related reactions and anaphylaxis, have been reported. Administer in a setting where severe hypersensitivity reactions can be managed. Monitor patients during the infusion and observe for at least 1 hour after infusion.

#### adjunct experimental therapies

- Treatment recommended for SOME patients in selected patient group

  » Consider any appropriate experimental or emerging therapies.

  » Antiviral therapies will have a greater effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies are likely to have a greater effect later in the course of the disease.[19]

  » Janus kinase inhibitors are recommended in certain patients; however, international guidelines vary in their recommendations.

  » See the Emerging section for more information.

#### adjunct plan for discharge and rehabilitation

- Treatment recommended for SOME patients in selected patient group

  » Routinely assess older patients for mobility, functional swallow, cognitive impairment, and mental health concerns. Based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[87]

#### adjunct palliative care

- Treatment recommended for SOME patients in selected patient group

  » Palliative care interventions should be made accessible at each institution that provides care.
**Acute**

for patients with COVID-19. Identify whether the patient has an advance care plan and respect the patient’s priorities and preferences when formulating the patient’s care plan.[87] Follow local palliative care guidelines.

» There are a lack of data on palliative care in patients with COVID-19. A rapid systematic review of pharmacologic strategies used for palliative care in these patients, the first international review of its kind, found that a higher proportion of patients required continuous subcutaneous infusions for medication delivery than is typically seen in the palliative care population. Modest doses of commonly used end-of-life medications were required for symptom control. However, these findings should be interpreted with caution due to the lack of data available.[855]

**critical COVID-19**

<table>
<thead>
<tr>
<th>1st intensive/critical care unit admission</th>
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<tbody>
<tr>
<td>» Admit or transfer patients with critical disease (i.e., presence of acute respiratory distress syndrome, sepsis, or septic shock) to an intensive/critical care unit under the guidance of a specialist team.[87]</td>
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</table>

» Discuss the risks, benefits, and potential outcomes of treatment options with patients and their families, and allow them to express preferences about their management. Take their wishes and expectations into account when considering the ceiling of treatment. Use decision support tools if available. Put treatment escalation plans in place, and discuss any existing advance care plans or advance decisions to refuse treatment with patients who have preexisting advanced comorbidities.[20]

» Implement local infection prevention and control procedures when managing patients with COVID-19.

» Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as midwifery and mental health and psychosocial support. A woman-centered, respectful, skilled approach to care is recommended.[87] The multidisciplinary team should be organized as soon as possible after maternal hypoxemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.[895]
### Acute

« Guidance on when to stop isolation varies widely across locations. Isolation periods may depend on various factors including vaccination status, circulating SARS-CoV-2 variants, and patient factors (e.g., immunocompetent/immunocompromised, asymptomatic/symptomatic, disease severity). The World Health Organization recommends discontinuing transmission-based precautions (including isolation) and releasing patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms. However, this guidance varies and you should consult your local public health guidance for more information.

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<tr>
<th>plus</th>
<th>symptom management and supportive care</th>
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<td></td>
<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td></td>
<td>Consider fluid and electrolyte management, antimicrobial treatment, and symptom management as appropriate. See Severe COVID-19 above for more detailed information.</td>
</tr>
<tr>
<td></td>
<td>Follow local guidelines for the management of pain, sedation, and delirium.</td>
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<td></td>
<td>Implement standard interventions to prevent complications associated with critical illness.</td>
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<tr>
<th>plus</th>
<th>venous thromboembolism prophylaxis</th>
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<tr>
<td></td>
<td>Treatment recommended for ALL patients in selected patient group</td>
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</table>

**Primary options**

« enoxaparin: consult specialist for guidance on dose

OR

« dalteparin: consult specialist for guidance on dose

**Secondary options**

« heparin: consult specialist for guidance on dose

OR

« fondaparinux: consult specialist for guidance on dose

« Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalized adults
and adolescents, provided there are no contraindications.[87] [19] [825] [826]

» Recommendations for patients with critical disease may differ from those for severe disease (see above). Consult your local guidelines.

» In the UK, the National Institute for Health and Care Excellence recommends a prophylactic dose of a low molecular weight heparin to young people and adults who need high-flow nasal oxygen, continuous positive airway pressure, noninvasive ventilation, or invasive mechanical ventilation, and who do not have an increased bleeding risk. An intermediate or treatment dose of a low molecular weight heparin is only recommended in these patients as part of a clinical trial.[20]

» In the US, the National Institutes of Health guidelines panel recommends prophylactic-dose heparin (low molecular weight heparin preferred over unfractionated heparin) for patients who are receiving intensive care unit level of care (including patients receiving high-flow oxygen), unless there is a contraindication. The panel recommends against the use of intermediate-dose and therapeutic-dose anticoagulation in these patients, except in the context of a clinical trial. Patients who start on therapeutic-dose heparin while in a non-intensive care unit setting and then transfer to the intensive care unit should be switched from therapeutic to prophylactic-dose heparin unless venous thromboembolism is confirmed.[19]

» Some guidelines recommend that escalated doses can be considered in critically ill patients.[825] [891]

» Dose adjustments may be required in patients with extremes of body weight or renal impairment.[20]

» Evidence is limited in patients with critical disease. A systematic review and meta-analysis of nearly 28,000 hospitalized patients found that both intermediate-dose and therapeutic-dose anticoagulation decreased the risk of thrombotic events in critically ill patients in the intensive care unit compared with prophylactic-dose anticoagulation, but these regimens were associated with an increased bleeding risk and unchanged in-hospital mortality.[892]

» See Severe COVID-19 above for more detailed information on VTE prophylaxis.
Acute

plus consider high-flow nasal oxygen or noninvasive ventilation

Treatment recommended for ALL patients in selected patient group

» Consider a trial of high-flow nasal oxygen (HFNO) or noninvasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in selected patients with mild acute respiratory distress syndrome. Patients with hypercapnia, hemodynamic instability, multi-organ failure, or abnormal mental status should generally not receive HFNO, although emerging data suggest that it may be safe in patients with mild to moderate and nonworsening hypercapnia. Patients with hypoxemic respiratory failure and hemodynamic instability, multi-organ failure, or abnormal mental status should not receive these treatments in place of other options such as invasive ventilation.[87]

» In the UK, the National Institute for Health and Care Excellence recommends CPAP in patients with hypoxemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of ≥0.4 (40%), and escalation to invasive mechanical ventilation would be an option but it is not immediately needed or it is agreed that respiratory support should not be escalated beyond CPAP. Ensure there is access to critical care providers for advice, regular review, and prompt escalation of treatment if needed, and regular assessment and management of symptoms alongside noninvasive respiratory support. Consider using HFNO for people when: they cannot tolerate CPAP but need humidified oxygen at high flow rates; maximal conventional oxygen is not maintaining their target oxygen saturations and they do not need immediate invasive mechanical ventilation or escalation to invasive mechanical ventilation is not suitable, and CPAP is not suitable; or they need a break from CPAP (e.g., mealtimes, skin pressure relief, mouth care), need humidified oxygen or nebulizers (or both), or need weaning from CPAP. Do not routinely offer HFNO as the main form of respiratory support for people with respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate.[20]

» In the US, the National Institutes of Health guidelines panel recommends HFNO over noninvasive ventilation in patients with acute hypoxemic respiratory failure despite conventional oxygen therapy. The panel recommends a closely monitored trial of
Acute noninvasive ventilation if HFNO is not available.[19]

- Airborne precautions are recommended for these interventions (including bubble CPAP) due to uncertainty about the potential for aerosolization.[87] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[908]

- Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require HFNO or noninvasive ventilation.[87] In the UK, the National Institute for Health and Care Excellence recommends considering awake prone positioning for hospitalized patients who are not intubated and have higher oxygen needs.[20] In the US, the National Institutes of Health guidelines panel recommends a trial of awake prone positioning in patients with persistent hypoxemia who require HFNO and for whom endotracheal intubation is not otherwise indicated. The panel recommends against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and invasive mechanical ventilation.[19] Awake prone positioning of nonintubated patients was associated with improvement in oxygen variables (PaO₂/FiO₂, PaO₂, and SpO₂), respiratory rate, rate of intubation (particularly among those who required advanced respiratory support and those in intensive care unit settings), and mortality. However, evidence is limited.[817][818][819][820]

- Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions, they require urgent endotracheal intubation.[87][816]

- Limited evidence suggests that noninvasive ventilation reduces the need for intubation, improves resource utilization, may be associated with better outcomes, and is safe.[865] There is no certain evidence that noninvasive respiratory support increases or decreases mortality in patients with COVID-19 acute respiratory failure.[864] Indirect and low-certainty evidence suggests that noninvasive ventilation probably reduces mortality in patients with COVID-19, similar to invasive mechanical ventilation, but may increase the risk of viral transmission. HFNO may reduce mortality compared with no HFNO.[866] HFNO was superior to noninvasive
ventilation for acute respiratory failure in terms of decreasing mortality. However, there was no significant difference in intubation rates and length of hospital stay between the two groups.[868] [869] The RECOVERY-RS trial (an open-label, multicenter, adaptive randomized controlled trial) found that CPAP reduced the need for invasive mechanical ventilation in adults admitted to hospital with acute respiratory failure. Neither CPAP nor HFNO reduced mortality when compared with conventional oxygen therapy.[870]

plus consider invasive mechanical ventilation

Treatment recommended for ALL patients in selected patient group

» Consider endotracheal intubation and mechanical ventilation in patients who are acutely deteriorating despite advanced oxygen/noninvasive ventilatory support measures.[87] [19]

» Endotracheal intubation should be performed by an experienced provider using airborne precautions.[87] Intubation by video laryngoscopy is recommended if possible.[19] Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require preoxygenation with 100% fraction of inspired oxygen (FiO₂) for 5 minutes.[87]

» Mechanically ventilated patients with acute respiratory distress syndrome (ARDS) should receive a lung-protective, low tidal volume/low inspiratory pressure ventilation strategy (lower targets are recommended in children). A higher positive end-expiratory pressure (PEEP) strategy is preferred over a lower PEEP strategy in moderate to severe ARDS. However, individualization of PEEP, where the patient is monitored for beneficial or harmful effects and driving pressure during titration with consideration of the risks and benefits of PEEP titration, is recommended.[87] [19] [816]

» Although some patients with COVID-19 pneumonia meet the criteria for ARDS, there is some discussion about whether COVID-19 pneumonia is its own specific disease with atypical phenotypes. Anecdotal evidence suggests that the main characteristic of the atypical presentation is the dissociation between well-preserved lung mechanics and the severity of hypoxemia.[874] [875] [876] [877] [878] [879] However, this approach has been criticized.[880] [881] Results from three large observational
cohort studies with data from critically ill patients with acute respiratory failure found that COVID-19-related ARDS had no consistent respiratory subphenotype at baseline (start of invasive ventilation). However, time-dependent analysis showed that two subphenotypes developed during the first 4 days of mechanical ventilation. Patients with an upward trajectory of ventilatory ratio had a higher risk of venous thrombotic events, more frequently developed acute kidney injury, required longer invasive mechanical ventilation, and had higher mortality.[882] It has been argued that an evidence-based approach extrapolating data from ARDS not related to COVID-19 is the most reasonable approach for intensive care of COVID-19 patients.[883] As a consequence of this, some clinicians have warned that protocol-driven ventilator use may be causing lung injury in some patients, and that ventilator settings should be based on physiologic findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.[874] PEEP should always be carefully titrated.[884]

» Consider prone ventilation in patients with severe ARDS for 12 to 16 hours per day. Pregnant women in the third trimester may benefit from being placed in the lateral decubitus position. Caution is required in children.[87] [19] [816] Longer durations may be feasible in some patients.[885]

» Lung recruitment maneuvers are suggested, but staircase recruitment maneuvers are not recommended.[19] [816]

adjunct inhaled pulmonary vasodilator

Treatment recommended for SOME patients in selected patient group

» Consider a trial of an inhaled pulmonary vasodilator in adults who have severe acute respiratory distress syndrome and hypoxemia despite optimizing ventilation. Taper off if there is no rapid improvement in oxygenation.[19] [816]

adjunct extracorporeal membrane oxygenation

Treatment recommended for SOME patients in selected patient group

» Consider extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[87] [816] [886]
Acute

» There is insufficient evidence to recommend either for or against the routine use of ECMO.[19]

» A systematic review and meta-analysis found that in-hospital mortality in adults receiving ECMO was 39%, and the risk of mortality was higher when compared with influenza patients on ECMO (44% versus 38%).[887]

» A registry-based cohort study found that ECMO was associated with a 7.1% reduction in mortality in selected adults (i.e., PaO₂/ FiO₂ <80 mmHg) with COVID-19-associated respiratory failure, compared with conventional mechanical ventilation without ECMO. It was most effective in patients ages <65 years and those with a PaO₂/FiO₂ <80 mmHg or with driving pressures >15 cm H₂O during the first 10 days of mechanical ventilation.[888]

» Single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure.[889]

» There is a risk of neurologic complications (e.g., intracranial hemorrhage, ischemic stroke, and hypoxic ischemic brain injury) in patients on ECMO.[890]

adjunct management of sepsis/septic shock

Treatment recommended for SOME patients in selected patient group

» The management of sepsis and septic shock in patients with COVID-19 is beyond the scope of this topic. See the Complications section.

adjunct corticosteroid

Treatment recommended for SOME patients in selected patient group

Primary options

» dexamethasone: children: consult specialist for guidance on dose; adults: 6 mg orally/intravenously once daily for 7-10 days

OR

» hydrocortisone: children: consult specialist for guidance on dose; adults: 50 mg orally/intravenously every 8 hours for 7-10 days

Secondary options
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» prednisone: children: consult specialist for guidance on dose; adults: 40 mg/day orally given in 1-2 divided doses for 7-10 days

**OR**

» methylprednisolone: children: consult specialist for guidance on dose; adults: 32 mg/day orally/intravenously given in 1-2 divided doses for 7-10 days

» Consider a systemic corticosteroid. Guideline recommendations vary.

» The World Health Organization (WHO) strongly recommends systemic corticosteroid therapy (low-dose intravenous or oral dexamethasone or hydrocortisone) for 7 to 10 days in adults with critical disease. This recommendation is based on two meta-analyses that pooled data from eight randomized trials (over 7000 patients), including the UK RECOVERY trial. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with critical disease. They also probably reduce the need for invasive ventilation. There is no evidence directly comparing dexamethasone and hydrocortisone. The harms of treatment in this context are considered to be minor. It is unclear whether these recommendations can be applied to children or those who are immunocompromised. [21] [795] [796] [839] [840] There is also evidence that corticosteroids probably increase ventilator-free days (moderate certainty). [848] [849]

» [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19] (https://www.bmj.com/content/370/bmj.m3379)

» In the UK, the National Institute for Health and Care Excellence recommends offering dexamethasone (or an alternative such as hydrocortisone or prednisone when dexamethasone cannot be used or is unavailable) to people who need supplemental oxygen to meet their prescribed oxygen saturation levels, or who have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. Treatment is for up to 10 days unless there is a clear indication to stop early. [20]

» In the US, the National Institutes of Health guidelines panel recommends using dexamethasone, either alone or in combination with remdesivir, in hospitalized
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**Primary options**

- **remdesivir**: children ≥12 years of age and ≥40 kg and adults: 200 mg intravenously as a loading dose on day 1, followed by 100 mg every 24 hours for 5-10 days

» Consider the antiviral agent remdesivir. Guideline recommendations vary, and there are moderate- and low-certainty evidence supports the use of corticosteroids in hospitalized patients. A Cochrane review found that systemic corticosteroids probably slightly reduce all-cause mortality in hospitalized patients with symptomatic disease. Most participants in the studies were treated with noninvasive or invasive mechanical ventilation. Low-certainty evidence suggests that there may also be a reduction in ventilator-free days; however, the current evidence remains uncertain due to methodological limitations. Evidence of an increased risk of mortality in symptomatic hospitalized patients without any need for additional oxygen was limited by a lack of statistical significance. It is unknown which systemic corticosteroid is most effective.

» Monitor patients for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.

» A meta-analysis found an increased risk of venous thromboembolism with corticosteroid administration in patients with critical disease. However, no definite findings were available due to the differing corticosteroid regimens and the heterogeneity of the studies.

» Monitor patients for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.

» A meta-analysis found an increased risk of venous thromboembolism with corticosteroid administration in patients with critical disease. However, no definite findings were available due to the differing corticosteroid regimens and the heterogeneity of the studies.
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conflicting recommendations across international guidelines. Remdesivir may increase the risk of death in critically ill patients, and currently only US guidelines recommend its use in select patients.

» In the US, the National Institutes of Health guidelines panel recommends remdesivir, in combination with dexamethasone, in hospitalized patients who require high-flow oxygen or noninvasive ventilation. The panel does not recommend starting remdesivir in patients who require invasive mechanical ventilation or extracorporeal membrane oxygenation. However, the panel does recommend completing the full treatment course of remdesivir if the patient is started on it when they are on supplemental low-flow oxygen (see Severe COVID-19 above) and then progress to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation. Remdesivir is approved in pediatric patients ≥28 days of age (weighing at least 7 lbs [3 kg]) in the US.

» In the UK, the National Institute for Health and Care Excellence recommends against the use of remdesivir in hospitalized patients on high-flow nasal oxygen, continuous positive airway pressure, noninvasive mechanical ventilation, or invasive mechanical ventilation, except as part of a clinical trial. Evidence shows that remdesivir may increase the risk of death in people who are on these interventions (moderate certainty).

» The World Health Organization recommends against the use of remdesivir in hospitalized patients in addition to standard care, regardless of disease severity. However, this recommendation is currently being reviewed, with an updated recommendation expected soon.

» If used, the recommended treatment course for this indication is 5 days or until hospital discharge, whichever comes first. Evidence does not suggest any greater benefit with a 10-day course of remdesivir compared with a 5-day course, but suggests an increased risk of harm. However, some experts may recommend a 10-day course in patients who have not shown substantial clinical improvement by day 5.

» Adverse effects include nephrotoxicity and hepatotoxicity. Remdesivir is not recommended in patients with an estimated glomerular filtration rate <30 mL/minute. Monitor renal
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Function before starting treatment and during treatment as clinically appropriate. Intravenous formulations contain the solubility enhancer sulfobutyl ether beta-cyclodextrin sodium (SBECD), which is renally cleared. Accumulation of SBECD in patients with renal impairment may result in liver and renal toxicities. Consider preferential use of the lyophilized powder formulation in patients with renal impairment if available, as it contains less SBECD. Remdesivir may have little or no effect on acute kidney injury compared with placebo; however, the certainty of evidence is low.[906] Transaminase elevations have been reported. Monitor liver function before starting treatment and during treatment as clinically appropriate. Consider discontinuing treatment if alanine aminotransferase (ALT) levels increase to ≥10 times the upper limit of normal. Discontinue treatment if ALT elevation is accompanied by signs or symptoms of liver inflammation. Monitor prothrombin time before starting treatment and during treatment as clinically appropriate as increases in prothrombin time have been reported.

- Hypersensitivity reactions, including infusion-related reactions and anaphylaxis, have been reported. Administer in a setting where severe hypersensitivity reactions can be managed. Monitor patients during the infusion and observe for at least 1 hour after infusion.

**Adjunct interleukin-6 (IL-6) inhibitor**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **tocilizumab:** children: consult specialist for guidance on dose; adults: 8 mg/kg intravenously as a single dose, maximum 800 mg/dose
  
  Typically administered as a single intravenous dose; however, a second dose may be administered 12 to 48 hours after the first dose if the clinical response is inadequate.


OR

- **sarilumab:** children: consult specialist for guidance on dose; adults: 400 mg intravenously as a single dose
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Typically administered as a single intravenous dose; however, a second dose may be administered 12 to 48 hours after the first dose if the clinical response is inadequate. World Health Organization. Therapeutics and COVID-19: living guideline. 2022 [internet publication]. https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.3

» Consider an IL-6 inhibitor. Guideline recommendations vary.

» The World Health Organization strongly recommends an IL-6 inhibitor (tocilizumab or sarilumab), in combination with a systemic corticosteroid and initiated at the same time, in patients with critical disease. This recommendation is based on high-certainty evidence that shows IL-6 inhibitors reduce mortality and the need for mechanical ventilation, and low-certainty evidence that suggests that IL-6 inhibitors may also reduce the duration of mechanical ventilation and hospitalization. The evidence regarding the risk of severe adverse events is uncertain. The applicability of this recommendation to children is currently uncertain.[21] [795] [796] This recommendation is based on data from the UK RECOVERY and REMAP-CAP trials.[845] [846]

» [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19] (https://www.bmj.com/content/370/bmj.m3379)

» In the US, the National Institutes of Health guidelines panel recommends adding tocilizumab to dexamethasone (or a suitable alternative corticosteroid) or dexamethasone plus remdesivir in patients who require noninvasive mechanical ventilation or high-flow nasal oxygen and have been recently hospitalized (e.g., within 3 days) with rapidly increasing oxygen needs and systemic inflammation. In patients who are on mechanical ventilation or extracorporeal membrane oxygenation, the panel recommends adding tocilizumab to dexamethasone for patients who are within 24 hours of admission to the intensive care unit. There is insufficient evidence for the panel to recommend either for or against the use of tocilizumab in hospitalized children. Sarilumab may be used as an alternative if tocilizumab is not available or it is not feasible to use it.[19] The Infectious Diseases Society of America recommends considering tocilizumab in hospitalized adults with critical disease who have elevated markers of systemic inflammation, in addition to standard of care (i.e., corticosteroids),
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rather than standard of care alone. Sarilumab may be used if tocilizumab is not available.[510]

» IL-6 inhibitors and Janus kinase inhibitors inhibitors (see table below) are viewed as alternatives to each other and should not be administered together. There is potential for an additive risk of infection.

» Patients on IL-6 inhibitors are at increased risk of infection including active tuberculosis, invasive fungal infections, and opportunistic pathogens.

» Routine blood work including neutrophil count, platelets, transaminases, and total bilirubin should be checked prior to initiation of therapy. All patients should be monitored for signs and symptoms of infection given the increased risk of immunosuppression in addition to systemic corticosteroids.[21]

» These drugs should be avoided in patients who are significantly immunocompromised.[19]

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**Primary options**

» **baricitinib**: children: consult specialist for guidance on dose; adults: 4 mg orally once daily for 14 days

**Secondary options**

» **tofacitinib**: children and adults: consult specialist for guidance on dose

OR

» **ruxolitinib**: children and adults: consult specialist for guidance on dose

» Consider a JAK inhibitor. Guideline recommendations vary.

» The World Health Organization strongly recommends a JAK inhibitor (baricitinib), in combination with a systemic corticosteroid and initiated at the same time, in patients with critical disease. This recommendation is based on moderate-certainty evidence that baricitinib probably reduces mortality and duration of mechanical ventilation, and high-certainty evidence that baricitinib reduces length of hospital stay. The applicability of
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this recommendation to children is currently uncertain.[21] [795] [796]

» [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19] (https://www.bmj.com/content/370/bmj.m3379)

» In the UK, the National Institute for Health and Care Excellence recommends baricitinib in hospitalized adults who: need supplemental oxygen (or other respiratory support including high-flow nasal oxygen, continuous positive airway pressure, noninvasive ventilation, or mechanical ventilation), and are having or have completed a course of corticosteroids (unless contraindicated), and have no evidence of infection (other than SARS-CoV-2) that might be worsened by baricitinib. Baricitinib may also be considered in children ≥2 years of age provided they meet the same criteria.[20]

» In the US, the National Institutes of Health guidelines panel recommends adding baricitinib to dexamethasone (or a suitable alternative corticosteroid) or dexamethasone plus remdesivir in patients who require noninvasive mechanical ventilation or high-flow nasal oxygen and have been recently hospitalized with rapidly increasing oxygen needs and systemic inflammation.[19] The Infectious Diseases Society of America suggests baricitinib in hospitalized adults (in combination with a corticosteroid) with severe disease. It suggests baricitinib with remdesivir, rather than remdesivir alone, in patients who cannot receive a corticosteroid because of a contraindication.[510]

» Other drugs in this class include tofacitinib and ruxolitinib. The World Health Organization recommends against using these drugs unless baricitinib or IL-6 inhibitors are not available. The effects of tofacitinib or ruxolitinib on mortality, need for mechanical ventilation, and hospital length of stay remain uncertain and more trial evidence is needed.[21] [795] [796] In the US, the National Institutes of Health guidelines panel recommends tofacitinib only if baricitinib is not available or it is not feasible to use it.[19] The Infectious Diseases Society of America suggests tofacitinib in hospitalized adults with severe disease who are not on noninvasive or invasive mechanical ventilation.[510]

» Evidence to support the use of baricitinib in critically ill patients is emerging. An exploratory, randomized, placebo-controlled trial found that baricitinib (in combination with standard
Acute care, including corticosteroids) reduced 28-day all-cause mortality (19% absolute reduction) and 60-day all-cause mortality (17% absolute reduction) in critically ill hospitalized patients who were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation compared with placebo. Further phase 3 trials are needed to confirm these findings as this was a small sample.[894]

» JAK inhibitors and IL-6 inhibitors (see table above) are viewed as alternatives to each other and should not be administered together. There is potential for an additive risk of infection.

» Patients are at increased risk of infection including active tuberculosis, invasive fungal infections, and opportunistic pathogens.[21] Avoid use in patients with known active tuberculosis. All patients should be monitored for signs and symptoms of infection given the increased risk of immunosuppression in addition to systemic corticosteroids. Monitor complete blood count with differential before and during treatment.

» Baricitinib is not recommended in patients with severe renal or hepatic impairment.[21] Baricitinib is not recommended in adults with an estimated glomerular filtration rate ≤15 mL/minute (≤30 mL/minute in children <9 years of age), or in patients on dialysis or renal replacement therapy. A dose reduction is recommended in patients with an estimated glomerular filtration rate ≤60 mL/minute. Baricitinib has not been studied in patients with severe hepatic impairment and it is unknown whether a dose adjustment is required in these patients. It should only be used if the potential benefits outweigh the potential risks. Use caution with tofacitinib and ruxolitinib in patients with moderate to severe renal impairment (including those on dialysis); a dose adjustment may be required. Monitor renal and hepatic function before and during treatment.

» Adverse effects include leukopenia, lymphopenia, thrombocytosis, anemia, blood clotting abnormalities, hepatic impairment, and secondary infection.[21] Other serious adverse effects include venous thrombosis and severe infections. The US Food and Drug Administration has issued a warning about increased risk of serious heart-related events, cancer, blood clots, and death with JAK inhibitors.[907]
**Acute**

Treatment recommended for SOME patients in selected patient group

- Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.[87] The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection. Start empiric treatment with oseltamivir in hospitalized patients who are suspected of having either or both infections as soon as possible without waiting for influenza test results. Antiviral therapy can be stopped once influenza has been ruled out.[19]

adjunct monoclonal antibody

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **casirivimab and imdevimab**: children ≥12 years of age and adults: consult specialist for guidance on dose

- Consider a monoclonal antibody. Guideline recommendations vary.

- The World Health Organization recommends casirivimab/imdevimab for patients with critical disease with a seronegative status (i.e., no detectable SARS-CoV-2 antibodies). Casirivimab/imdevimab should only be used where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e., excluding Omicron). Casirivimab/imdevimab probably reduces mortality and possibly reduces the need for mechanical ventilation in patients who are seronegative based on moderate- and low-certainty evidence, respectively. Treatment is in addition to the current standard of care. The applicability of this recommendation to children is currently uncertain.[21][795][796]

- [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19](https://www.bmj.com/content/370/bmj.m3379)

  Monoclonal antibodies are administered by intravenous infusion. Casirivimab/imdevimab is also available in a subcutaneous formulation, but intravenous administration is recommended. However, if intravenous infusions are not feasible or would cause a delay in treatment, subcutaneous administration may be considered.[19] Dose varies across guidelines; consult local protocols.

- Circulating SARS-CoV-2 variants may be associated with resistance to monoclonal
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antibodies. Data suggests that the efficacy of casirivimab/imdevimab is likely to be compromised against the Omicron variant.[19] [20] Consult local guidance for details regarding specific variants and resistance.

» Hypersensitivity reactions, including infusion-related reactions and anaphylaxis, have been reported. Administer in a setting where severe hypersensitivity reactions can be managed. Monitor patients during the infusion and observe for at least 1 hour after infusion.

» Logistical or supply constraints may make patient triage for monoclonal antibody treatment necessary.

**adjunct** experimental therapies

Treatment recommended for SOME patients in selected patient group

» Consider any appropriate experimental or emerging therapies.

» Antiviral therapies will have a greater effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies are likely to have a greater effect later in the course of the disease.[19]

» Janus kinase inhibitors are recommended in certain patients; however, international guidelines vary in their recommendations.

» See the Emerging section for more information.

**adjunct** plan for discharge and rehabilitation

Treatment recommended for SOME patients in selected patient group

» Routinely assess intensive care patients for mobility, functional swallow, cognitive impairment, and mental health concerns. Based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[87]

**adjunct** palliative care

Treatment recommended for SOME patients in selected patient group

» Palliative care interventions should be made accessible at each institution that provides care for patients with COVID-19. Identify whether the patient has an advance care plan and respect the patient’s priorities and preferences when
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formulating the patient’s care plan.[87] Follow local palliative care guidelines.

» There are a lack of data on palliative care in patients with COVID-19. A rapid systematic review of pharmacologic strategies used for palliative care in these patients, the first international review of its kind, found that a higher proportion of patients required continuous subcutaneous infusions for medication delivery than is typically seen in the palliative care population. Modest doses of commonly used end-of-life medications were required for symptom control. However, these findings should be interpreted with caution due to the lack of data available.[855]
Emerging

Nirmatrelvir/ritonavir

Nirmatrelvir is an experimental oral severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-3CL protease inhibitor antiviral drug. Coadministration with a low dose of ritonavir (which is commonly administered with other protease inhibitors as part of antiretroviral therapy for HIV infection) helps to slow the hepatic metabolism of nirmatrelvir so it remains active in the body for a longer period of time. Nirmatrelvir/ritonavir is authorized for use in some countries. The World Health Organization strongly recommends nirmatrelvir/ritonavir in adults with nonsevere disease who are at highest risk of hospitalization (e.g., older age, immunosuppression and/or chronic diseases, unvaccinated for COVID-19). It recommends against the use of nirmatrelvir/ritonavir in patients with nonsevere disease who are at low risk of hospitalization.[21] Nirmatrelvir/ritonavir should be initiated as soon as possible after diagnosis, ideally within 5 days of symptom onset. The treatment course is 5 days. It is not recommended in pregnant and breastfeeding women or children. A dose reduction is required in patients with renal impairment. Nirmatrelvir/ritonavir likely reduces hospital admission in patients with nonsevere disease (moderate-certainty evidence), and may have little or no impact on mortality (low-certainty evidence). Treatment does not increase the likelihood of adverse effects leading to drug discontinuation (high-certainty evidence). However, diarrhea and dysgeusia occur more frequently with nirmatrelvir/ritonavir compared with placebo. Nirmatrelvir/ritonavir is a superior choice to other treatments for nonsevere disease because it may have greater efficacy in preventing hospitalization compared with the alternatives, has fewer concerns with respect to harms than does molnupiravir, and is easier to administer than intravenous remdesivir and the monoclonal antibodies. The UK National Institute for Health and Care Excellence recommends considering nirmatrelvir/ritonavir in adults ≥18 years of age who do not need supplemental oxygen, and are within 5 days of symptom onset, and are thought to be at high risk of progression to severe disease.[20] The US National Institutes of Health guidelines panel recommends nirmatrelvir/ritonavir in nonhospitalized patients ≥12 years of age (weighing ≥40 kg) and adults with mild to moderate disease who are at high risk of disease progression. If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the healthcare provider’s discretion. The Infectious Diseases Society of America also recommends the use of nirmatrelvir/ritonavir in these patients.[510] Evidence is emerging. Evidence of clinical efficacy is based on an interim analysis of data from a single placebo-controlled trial in unvaccinated adults that was conducted before the emergence of the Omicron variant. Nirmatrelvir/ritonavir was found to reduce the risk of hospitalization or death by 89% (within 3 days of symptom onset) and 88% (within 5 days of symptom onset) compared with placebo in nonhospitalized high-risk adults in the phase 2/3 EPIC-HR randomized double-blind clinical trial.[909] Nirmatrelvir/ritonavir appears to retain activity against the Omicron variant and other variants of concern in vitro.[910] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug. Ritonavir-boosted nirmatrelvir has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination. Carefully review the patient’s medication history before starting treatment.

Molnupiravir

A prodrug that is metabolized to the ribonucleoside analog N-hydroxycytidine (NHC), which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP is incorporated into viral RNA by the viral RNA polymerase, resulting in an accumulation of errors in the viral genome leading to inhibition of replication. The World Health Organization conditionally recommends molnupiravir in adults with nonsevere disease who are at highest risk of hospitalization (e.g., older age, immunosuppression and/or chronic diseases, unvaccinated for COVID-19).[21] Molnupiravir should be initiated as soon as possible after diagnosis, ideally within 5 days of symptom onset. The treatment course is 5 days. It is not recommended in pregnant and breastfeeding women, or children. Animal studies have shown reproductive toxicity, and it may affect bone and cartilage growth. A pregnancy test should be performed prior to initiation of treatment. Contraception is recommended during treatment and for 4 days after the last dose in women of childbearing potential, and for at least 3 months after the last dose in men of reproductive potential who are sexually active with women of childbearing potential. Longer-term harms (e.g., genotoxicity, resistance) remain unknown in the absence of clinical evidence, both for individual patients and at the population level. The World Health Organization recommends active monitoring for drug safety, along with other strategies to mitigate potential harms as this is a new drug with very little safety data. Molnupiravir probably reduces hospital admission and time
Management of SARS-CoV-2 infection and related conditions

Anakinra

Anakinra is an intravenous/subcutaneous interleukin-1 inhibitor. It is being trialed in patients for the treatment of SARS-CoV-2-induced cytokine release syndrome. Anakinra is already approved in some countries for certain conditions, but is off-label for this indication. The European Medicines Agency has approved anakinra in adults with pneumonia who require low- or high-flow supplemental oxygen and who are at risk of developing severe respiratory failure, as determined by blood soluble urokinase plasminogen activator receptor (suPAR) levels of at least 6 nanograms/mL.[915] The UK National Institute for Health and Care Excellence states that there is no evidence available to determine whether anakinra is effective, safe, or cost-effective for treating adults and children with secondary hemophagocytic lymphohistiocytosis triggered by SARS-CoV-2 or a similar coronavirus.[916] The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of anakinra.[19] Evidence is emerging. Evidence of clinical efficacy is based on an interim analysis of data from a single placebo-controlled trial in unvaccinated adults that was conducted before the emergence of the Omicron variant. According to a press release from the manufacturer, anakinra significantly reduced the risk of hospitalization or death in the 29 days after use in at-risk, nonhospitalized, unvaccinated adults with mild to moderate disease in an analysis of the phase 3 MOVE-OUT trial (1433 patients). Molnupiravir reduced the relative risk of hospitalization or death by approximately 30% (absolute risk reduced from 9.7% to 6.8%).[911] This figure is less than the manufacturer’s original press release, which stated use of molnupiravir resulted in a 50% relative risk reduction based on an early interim analysis. Recruitment into the study was stopped early due to these positive results. However, the trial was underpowered to detect clinically important adverse effects and did not include children or pregnant women, and the trial population was unvaccinated and recruited before the most recent variants emerged. Final trial results are yet to be peer reviewed and published, but an interim analysis of earlier data has been published.[912] Results from the phase 2 portion of the study have also been published.[913] Two phase 1 double-blind, randomized, placebo-controlled trials showed that molnupiravir was safe and tolerable without any serious adverse effects. A phase 2 study found that molnupiravir significantly lowered time to viral clearance in patients with mild to moderate disease compared with placebo. However, it was not effective in moderate to severe disease. Several phase 3 trials are ongoing. There are no data evaluating the role of molnupiravir in breakthrough infections following vaccination.[914] Molnupiravir appears to retain activity against the Omicron variant and other variants of concern in vitro.[910] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

to symptom resolution (moderate-certainty evidence), and may reduce mortality (low-certainty evidence), but effect on mechanical ventilation is very uncertain (very low-certainty evidence). The conditional recommendation reflects the concern for widespread treatment with molnupiravir before more safety data become available. The UK National Institute for Health and Care Excellence recommends considering molnupiravir in adults ≥18 years of age who do not need supplemental oxygen, and are within 5 days of symptom onset, and are thought to be at high risk of progression to severe disease.[20] The US National Institutes of Health guidelines panel recommends molnupiravir in nonhospitalized adults ≥18 years of age with mild to moderate disease who are at high risk of disease progression, only when preferred therapies are not available, feasible to use, or clinically appropriate. If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the healthcare provider’s discretion.[19] The Infectious Diseases Society of America also recommends the use of molnupiravir in these patients.[510] Evidence is emerging. Evidence of clinical efficacy is based on an interim analysis of data from a single placebo-controlled trial in unvaccinated adults that was conducted before the emergence of the Omicron variant. According to a press release from the manufacturer, molnupiravir significantly reduced the risk of hospitalization or death in the 29 days after use in at-risk, nonhospitalized, unvaccinated adults with mild to moderate disease in an analysis of the phase 3 MOVE-OUT trial (1433 patients). Molnupiravir reduced the relative risk of hospitalization or death by approximately 30% (absolute risk reduced from 9.7% to 6.8%).[911] This figure is less than the manufacturer’s original press release, which stated use of molnupiravir resulted in a 50% relative risk reduction based on an early interim analysis. Recruitment into the study was stopped early due to these positive results. However, the trial was underpowered to detect clinically important adverse effects and did not include children or pregnant women, and the trial population was unvaccinated and recruited before the most recent variants emerged. Final trial results are yet to be peer reviewed and published, but an interim analysis of earlier data has been published.[912] Results from the phase 2 portion of the study have also been published.[913] Two phase 1 double-blind, randomized, placebo-controlled trials showed that molnupiravir was safe and tolerable without any serious adverse effects. A phase 2 study found that molnupiravir significantly lowered time to viral clearance in patients with mild to moderate disease compared with placebo. However, it was not effective in moderate to severe disease. Several phase 3 trials are ongoing. There are no data evaluating the role of molnupiravir in breakthrough infections following vaccination.[914] Molnupiravir appears to retain activity against the Omicron variant and other variants of concern in vitro.[910] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.
Colchicine

Colchicine is an anti-inflammatory agent that downregulates multiple pro-inflammatory pathways. It is thought that its inhibitory effects on neutrophil activity, cytokine generation, and the inflammation/thrombosis interface, along with an overall lack of evidence for systemic immunosuppression, make it a useful treatment.[921] Colchicine is already approved in some countries for indications such as gout and familial Mediterranean fever, but is off-label for this indication. The UK National Institute for Health and Care Excellence does not recommend the use of colchicine. Evidence in hospitalized patients and community settings found no benefit of effect on hospitalization, recovery time, all-cause mortality, mechanical ventilation, clinical progression, intensive care unit admission, or hospital discharge within 28 days.[20] The US National Institutes of Health guidelines panel recommends against the use of colchicine for the treatment of hospitalized patients, and against its use in nonhospitalized patients except in the context of a clinical trial.[19] Evidence does not currently support the use of this treatment. A Cochrane review found that the use of colchicine probably has little to no influence on mortality or clinical progression in hospitalized patients with moderate to severe disease, compared with placebo or standard care alone (moderate-certainty evidence). Evidence for effect on all-cause mortality for people with asymptomatic or mild disease is uncertain; however, use probably results in a slight reduction in hospital admissions or 28-day mortality.[922] A living systematic review and network meta-analysis found that colchicine may reduce mortality (low-certainty evidence) and probably reduces the duration of hospitalization (low-certainty evidence) compared with standard care.[848] [849] The largest meta-analysis to date (approximately 16,000 patients), which included six randomized controlled trials, found that colchicine did not significantly reduce mortality, need for ventilatory support, intensive care unit admission, or length of hospital stay compared with supportive care only, and patients taking colchicine had a higher risk of adverse events. The GRADE quality of evidence was moderate for most outcomes.[923] The UK PRINCIPLE trial found that colchicine did not improve time to recovery in people in the community at higher risk of complications compared with usual care alone. There was also no evidence for a benefit in hospitalizations or deaths; however, estimates were imprecise due to the few hospitalizations in the trial.[924] The UK RECOVERY trial found that colchicine was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death in hospitalized adults.[925] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) inhibitors

GM-CSF inhibitors (e.g., lenzilumab, mavrilimumab, otilimab) may mitigate lung inflammation in severe and critical disease by minimizing downstream production of numerous pro-inflammatory mediators involved in the pathogenesis of disease. These agents are currently investigational. The US Food and Drug Administration has declined an emergency-use authorization for lenzilumab to treat hospitalized COVID-19 patients as it was unable to conclude that the known and potential benefits of lenzilumab outweigh the known and potential risks of its use.[926] The UK Medicines and Healthcare products Regulatory Agency is currently reviewing an application for a conditional marketing authorization for lenzilumab. The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of GM-CSF inhibitors.[19] Evidence is emerging. A phase 3, randomized, double-blind, placebo-controlled trial found that lenzilumab significantly improved survival without invasive mechanical ventilation to day 28 in hospitalized patients.[927] A small multicenter, double-blind, randomized, placebo-controlled trial found that there was no significant difference in the proportion of patients with severe disease, hypoxemia, and systemic hyperinflammation who were free of supplemental oxygen at day 14 after treatment with mavrilimumab compared with placebo.[928]

Convalescent plasma

Convalescent plasma is a blood product that contains antibodies to SARS-CoV-2 from patients who have recovered. High-titer convalescent plasma (i.e., plasma with high SARS-CoV-2 antibody titers) has been granted an emergency-use authorization in the US for the treatment of hospitalized patients early in the disease course, and to those hospitalized patients who have impaired humoral immunity and cannot produce an adequate antibody response. Low-titer convalescent plasma is no longer authorized.[929] It has not been authorized for this indication in the UK or Europe. The World Health Organization recommends against the use of convalescent plasma. The guideline recommends against using convalescent plasma in patients...
with nonsevere disease. In these patients, convalescent plasma did not result in an important impact on mortality, based on high-certainty evidence. Convalescent plasma probably did not impact mechanical ventilation, based on moderate-certainty evidence. There were no data evaluating the risk of hospitalization and therefore the impact is very uncertain. The guideline recommends against using convalescent plasma in patients with severe or critical disease, except in the context of a clinical trial. In these patients, convalescent plasma may not result in an important impact on mortality, mechanical ventilation, time to symptom improvement, length of hospital stay, or ventilator-free days, based on low-certainty evidence.[21][795][796] UK guidance recommends that convalescent plasma should not be used in the management of hospitalized patients with suspected or confirmed infection.[930] The US National Institutes of Health guidelines panel recommends against the use of convalescent plasma in hospitalized immunocompetent patients. The panel recommends against the use of convalescent plasma collected prior to the emergence of the Omicron variant. There is insufficient evidence to recommend either for or against the use of high-titer convalescent plasma collected after the emergence of the Omicron variant for the treatment of immunocompromised patients and nonhospitalized immunocompetent patients. Use in hospitalized children with impaired immunity may be considered on a case-by-case basis provided that they meet the emergency-use authorization criteria.[19] The Infectious Diseases Society of America recommends against the use of convalescent plasma in hospitalized patients, based on moderate-certainty evidence.[510] The guideline panel suggests Food and Drug Administration-qualified high-titer convalescent plasma for ambulatory patients with mild to moderate disease who are at high risk for progression to severe disease if they have no other treatment options, and within 8 days of symptom onset, based on low-certainty evidence. Evidence does not currently support the use of this treatment. A living systematic review and network meta-analysis found that convalescent plasma may not confer any meaningful benefit in patients with any disease severity. Whether or not high-titer convalescent plasma confers any benefit remains uncertain.[931] A Cochrane review found high-certainty evidence that convalescent plasma does not reduce mortality and has little to no impact on measures of clinical improvement for the treatment of moderate to severe disease.[932] Evidence from meta-analyses is conflicting. While some meta-analyses found that treatment with convalescent plasma was not significantly associated with a decrease in all-cause mortality (or any benefit for other outcomes) compared with placebo or standard of care, others have found a reduction in mortality, especially when trials with low-titer convalescent plasma were removed from the analyses.[933][934][935][936][937][938] A prospective individual patient data meta-analysis of international randomized controlled trials collaborating in the COMPILE study in hospitalized, noncritically ill patients found that convalescent plasma was associated with neither benefit nor harm consistently across trials.[939] The UK RECOVERY trial found that high-titer convalescent plasma did not improve 28-day mortality or other prespecified outcomes (hospital discharge within 28 days, progression to invasive mechanical ventilation) in hospitalized patients compared with usual care.[940] A randomized controlled trial found that administration of convalescent plasma to symptomatic adult outpatients (regardless of risk factors for disease progression or vaccination status) within 9 days of symptom onset reduced the risk of disease progression leading to hospitalization.[941] Patient factors may help identify which patients would benefit most from treatment with convalescent plasma. Patients with comorbidities (diabetes, cardiovascular and pulmonary diseases), with blood type A or AB, and at an early disease stage may benefit most, while those without preexisting conditions and at more advanced stages of disease could potentially be harmed.[942]

**Intravenous immune globulin**

Intravenous immune globulin (IVIG) is a blood product prepared from serum pooled from healthy donors. It has an immunomodulatory effect that suppresses a hyperactive immune response. IVIG is already approved in some countries for certain conditions, but is off-label for this indication. The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for or against the use of anti-SARS-CoV-2 specific immune globulin.[19] Evidence does not currently support the use of this treatment. A living systematic review and network meta-analysis found that IVIG may not confer any meaningful benefit in patients with any disease severity.[931] A meta-analysis of four clinical trials and three cohort studies with 825 hospitalized patients found that IVIG reduced mortality in patients with critical disease; however, there was no significant difference between the severe and nonsevere subgroups.[943] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

**Stem cell therapy**
Mesenchymal stem cells are an investigational product and have been studied for their immunomodulatory properties. It is thought that they can reduce the pathologic changes that occur in the lungs, and inhibit the cell-mediated immune inflammatory response.\[944\] Mesenchymal stem cells are not approved for this indication. The US National Institutes of Health guidelines panel recommends against the use of mesenchymal stem cells except in the context of a clinical trial.\[19\] Evidence is emerging. Systematic reviews and meta-analyses have found that mesenchymal stem cell therapy may reduce the incidence of adverse events and mortality; however, evidence is limited and further research is required.\[945\] \[946\] \[947\] Remestemcel-L (ex vivo cultured adult human mesenchymal stem cells from the bone marrow of healthy adult donors) is currently in phase 3 trials for the treatment of moderate to severe acute respiratory distress syndrome in ventilator-dependent patients. An interim analysis of data found that the trial is not likely to meet its 30-day mortality reduction end point and has stopped enrollment, although the trial will be completed with the patients currently enrolled, with follow-up as planned.\[948\]

**Interferons**

Interferons are a family of cytokines with antiviral properties. Interferons are already approved in some countries for certain conditions, but are off-label for this indication. The US National Institutes of Health guidelines panel recommends against the use of interferons for the treatment of hospitalized patients except in the context of a clinical trial. The panel recommends against the use of interferon beta for the treatment of hospitalized patients. The panel recommends against the use of interferon alfa or lambda for the treatment of hospitalized patients, except in the context of a clinical trial. The panel recommends against the use of interferon for the treatment of nonhospitalized patients with mild to moderate disease, except in the context of a clinical trial.\[19\] Evidence does not currently support the use of this treatment. The WHO Solidarity trial found that interferon beta-1a appears to have little or no effect on hospitalized patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.\[842\] A randomized, placebo-controlled, phase 2 trial found that nebulized interferon beta-1a was associated with a higher odds of clinical improvement and more rapid recovery.\[949\] A phase 2 trial found that peginterferon lambda reduced viral load and increased the number of participants with a negative nasopharyngeal swab at day 7 in outpatients with mild to moderate disease compared with placebo.\[950\] \[951\] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing these drugs.

**Ivermectin**

Ivermectin is a broad-spectrum antiparasitic agent. It has been shown to be effective against SARS-CoV-2 in vitro.\[952\] Ivermectin is already approved in some countries for parasitic infections, but is off-label for this indication. The World Health Organization does not recommend ivermectin except in the context of a clinical trial.\[21\] This recommendation applies to patients with any disease severity and any duration of symptoms. There is insufficient evidence to be clear to what extent, if any, ivermectin is helpful or harmful in treating COVID-19.\[795\] \[796\] For most key outcomes, including mortality, mechanical ventilation, hospital admission, duration of hospitalization, and viral clearance, the evidence is of very low certainty. The UK National Institute for Health and Care Excellence does not recommend ivermectin except as part of a clinical trial.\[20\] The US National Institutes of Health guidelines panel recommends against the use of ivermectin, except in the context of a clinical trial.\[19\] The Infectious Diseases Society of America suggests against the use of ivermectin in outpatients and hospitalized patients outside of the context of a clinical trial.\[510\] Evidence is emerging. A Cochrane review found no evidence to support the use of ivermectin for treating or preventing infection, but the evidence base was limited (as of 26 May 2021). The safety and efficacy of ivermectin was uncertain based on very low- to low-certainty evidence. Overall, the reliable evidence available does not support the use of ivermectin for treatment or prevention outside of well-designed randomized trials.\[953\] Data from meta-analyses are conflicting. A meta-analysis of 24 randomized controlled trials with 3400 participants found moderate-certainty evidence that ivermectin provided a significant survival benefit when used for treatment. Low-certainty evidence supports a likely clinical benefit in terms of improvement and deterioration. Low-certainty evidence also suggests a significant effect in prophylaxis. Overall, the evidence suggests that early use may reduce morbidity and mortality.\[954\] Other meta-analyses also support an improvement in clinical outcomes with use of ivermectin, although the quality of evidence is very low to low.\[955\] \[956\] \[957\] \[958\] \[959\] However, there are other meta-analyses that found that ivermectin did not reduce all-cause mortality, length of hospital stay, incidence of mechanical ventilation, time to clinical recovery, or respiratory viral clearance.\[959\] \[960\] \[961\] One meta-analysis found that strongyloidiasis prevalence interacts with the relative risk of mortality in ivermectin trials for the outcome of mortality, and no evidence was found to suggest that ivermectin had any role in preventing mortality in patients with COVID-19.
in regions where strongyloidiasis was not endemic.[962] One meta-analysis found that ivermectin was effective when used for pre-exposure prophylaxis in preventing transmission among healthcare workers in low- and middle-income countries; however, evidence was limited.[963] The PRINCIPLE trial in the UK is currently investigating the use of ivermectin.[964] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

**Nitazoxanide**

Nitazoxanide is a broad-spectrum antiparasitic agent with in vitro activity against SARS-CoV-2 that is already approved in some countries for indications such as cryptosporidiosis and giardiasis, but is off-label for this indication. The US National Institutes of Health guidelines panel recommends against the use of nitazoxanide except in the context of a clinical trial.[19] Evidence is emerging. A randomized, double-blind, placebo-controlled trial found that nitazoxanide may reduce the risk of progression to severe disease in outpatients with mild to moderate disease who are at high risk of disease progression, and reduce the time to sustained clinical recovery in patients with mild disease.[965] A randomized, double-blind pilot trial found an event decrease in the time for hospital discharge, faster evolution to reverse transcription polymerase chain reaction negativity, and a higher reduction of inflammatory markers among patients treated with nitazoxanide compared with placebo. However, this was a small, proof-of-concept trial.[966] A multicenter, randomized, double-blind, placebo-controlled trial in adults with mild disease found that nitazoxanide was associated with reduced viral load but not reduced time to symptom resolution.[967] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

**Fluvoxamine**

Fluvoxamine is a selective serotonin-reuptake inhibitor that has anti-inflammatory and possible antiviral effects.[968] Fluvoxamine is already approved in some countries for indications such as depression and obsessive compulsive disorder, but is off-label for this indication. The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of fluvoxamine.[19] The Infectious Diseases Society of America recommends fluvoxamine in ambulatory patients only in the context of a clinical trial.[510] Evidence is emerging. A meta-analysis of randomized controlled trials, including the TOGETHER trial (a randomized placebo-controlled trial with nearly 1500 participants), found that patients receiving fluvoxamine were less likely to experience clinical deterioration or hospitalization compared with placebo, although analysis of hospitalization-only data was not statistically significant.[969] The TOGETHER trial found that fluvoxamine reduced the need for hospitalization (5% absolute risk reduction) among high-risk patients compared with placebo.[970] A preliminary double-blind, randomized controlled trial found that adult outpatients had a lower likelihood of clinical deterioration over 15 days compared with placebo; however, the study was limited by a small sample size and short follow-up duration.[971] A prospective cohort study in the setting of a mass outbreak found that fluvoxamine may prevent clinical deterioration requiring hospitalization and symptoms persisting beyond 2 weeks.[972] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

**Inhaled corticosteroids**

Inhaled budesonide is undergoing clinical trials and shows promise.[973] It is thought to modulate the inflammatory pathways in the upper respiratory tract and circulation following infection.[974] Inhaled budesonide is already approved in some countries for indications such as asthma and COPD, but is off-label for this indication. The UK National Institute for Health and Care Excellence only recommends inhaled budesonide as part of a clinical trial. Trial evidence suggests some benefit in reducing time to recovery. However, evidence suggests there is no statistically significant difference for the outcomes of hospitalization and death, or need for mechanical ventilation in people having inhaled budesonide and usual care compared with usual care alone. Evidence is limited and further research is required.[20] The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of inhaled budesonide.[19] The Infectious Diseases Society of America suggests against inhaled corticosteroids in patients with mild to moderate disease, except in the context of a clinical trial.[510] Evidence is emerging. A Cochrane review found that inhaled corticosteroids (budesonide and ciclesonide) probably reduced the combined end point of admission to hospital or death and increased the resolution of initial symptoms at day 14 in people with mild symptoms (moderate-certainty evidence).
However, low-certainty evidence suggests that corticosteroids make little to no difference in all-cause 30-day mortality and may decrease duration to symptom resolution.[975] The PRINCIPLE trial has reported a 3-day median benefit in self-reported recovery for patients in the community setting who are at higher risk of complications and who received inhaled budesonide.[976] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

**Antibiotics**

Azithromycin is a macrolide antibiotic, and doxycycline is a tetracycline antibiotic. Both are approved for use in various bacterial infections. The UK National Institute for Health and Care Excellence does not recommend the use of azithromycin or doxycycline. The guideline panel considered that the results from studies of azithromycin for moderate to critical disease in the hospital setting and mild to moderate disease in the community setting showed no meaningful benefit in any of the critical outcomes.[20] The UK Medicines and Healthcare products Regulatory Agency recommends that azithromycin and doxycycline should not be used within primary care (or hospitalized patients for azithromycin) unless there are additional indications for which their use remains appropriate.[977] The US National Institutes of Health guidelines panel recommends against the use of antibacterial therapy (e.g., azithromycin, doxycycline) in the absence of another indication.[19] Evidence does not support the use of this treatment. A Cochrane review found that azithromycin did not reduce 28-day all-cause mortality in hospitalized patients compared with standard of care alone (high-certainty evidence). Hospitalized patients with moderate to severe disease did not benefit from azithromycin in terms of clinical worsening or improvement (moderate-certainty evidence). Azithromycin had no beneficial effect in the outpatient setting (low-certainty evidence).[978] Systematic reviews and meta-analyses have found that azithromycin was not associated with an improvement in hospitalization rate, intensive care unit admission, need for respiratory support, or mortality rate compared with control.[979] [980] The overall quality of evidence was low to very low. The UK RECOVERY trial found that azithromycin showed no significant clinical benefit (i.e., length of hospital stay, need for invasive mechanical ventilation, 28-day mortality) in hospitalized patients compared with usual standard care alone.[981] The UK PRINCIPLE trial found that doxycycline use was not associated with clinically meaningful reductions in time to recovery or hospital admissions or deaths in patients with suspected disease in the community who were at high risk of adverse outcomes.[982] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing these drugs.

**Vitamin D**

Vitamin D supplementation has been associated with a reduced risk of acute respiratory infections such as influenza.[983] [984] [985] [986] The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for or against vitamin D for the treatment or prevention of COVID-19.[19] The UK National Institute for Health and Care Excellence recommends vitamin D supplementation in adults (including pregnant and breastfeeding women), young people, and children over 4 years of age between October and early March (and at other times of the year if at risk of vitamin D deficiency) to maintain bone and muscle health. However, it does not recommend supplementation to solely prevent or treat COVID-19, except as part of a clinical trial.[977] Evidence is emerging. A Cochrane review found there is currently insufficient evidence to determine the benefits and harms of vitamin D supplementation. The evidence is very uncertain. There was substantial clinical and methodological heterogeneity of included studies, mainly due to different supplementation strategies, formulations, vitamin D status of participants, and reported outcomes.[988] Meta-analyses have found that vitamin D might be associated with improved clinical outcomes, including decreased risk of intensive care admission and mortality, and that there may be a potential role for vitamin D supplementation in reducing disease severity, but noted that additional evidence is required.[989] [990] [991] [992] [993] The evidence is currently insufficient to support the routine use of vitamin D as its effectiveness appears to depend on the dose used, baseline vitamin D levels, and the severity of disease.[994] A pilot randomized controlled trial found that high-dose calcifediol significantly reduced the need for intensive care unit treatment in hospitalized patients, and may improve clinical outcomes.[995]

**Vitamin C**

Vitamin C supplementation has shown promise in the treatment of viral infections.[996] High-dose intravenous vitamin C is being trialed in some centers for the treatment of severe disease.[997] The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for
or against vitamin C for the treatment of noncritically ill or critically ill patients.[19] Evidence is emerging. A systematic review of six randomized controlled trials found that vitamin C did not reduce mortality, length of stay in hospital or intensive care unit, or need for invasive mechanical ventilation. However, there were various limitations to the study (e.g., heterogeneity of dose and route). Further well-designed randomized controlled trials are required.[998] A systematic review and meta-analysis found that length of hospital stay and mortality was not significantly different between patients taking high-dose intravenous vitamin C and those not taking it. Evidence supporting the therapeutic use of high-dose intravenous vitamin C is lacking and further studies are required.[999]

**Lung transplantation**

Lung transplantation has been used as salvage therapy in patients with COVID-19–associated acute respiratory distress syndrome (ARDS) who do not recover despite maximum ventilatory support, extracorporeal membrane oxygenation, and optimal medical care. Between August 2020 and September 2021, 214 lung transplantations were performed in the US (7% of lung transplants nationally). The 3-month survival among these patients approached that among patients who underwent lung transplantation for reasons other than COVID-19.[1000] In a retrospective case series of 30 patients with COVID-19–associated ARDS who underwent lung transplantation, survival was 100% (median follow-up 351 days).[1001]

**Clinical trials**


**Primary prevention**

Vaccines

- The World Health Organization (WHO) has authorized the use of the following vaccines for global use:[338] [339] [340] [341] [342] [343] [344]
  - mRNA vaccines: Comirnaty® (Pfizer/BioNTech); Spikevax® (Moderna)
  - Adenovirus vector vaccines: Vaxzevria® (AstraZeneca); Ad26.COV2.S (Janssen)
  - Protein subunit vaccines: Nuvaxoid® (Novavax); Covovax® (Serum Institute of India)
  - Inactivated virus vaccines: Covilô® (Sinopharm); CoronaVac® (Sinovac)

- Vaccine availability and immunization programs differ between countries.

- Other vaccines have been authorized in specific countries (e.g., Valneva inactivated virus vaccine in the UK). Vaccines are generally available under emergency-use, provisional, or conditional marketing authorizations, but may be fully approved in some countries. Consult your local guidance for information.

- Patients must give informed consent prior to vaccination.

- For consent to immunization to be valid, it must be given freely, voluntarily, and without coercion by an appropriately informed person.[345]

- Protection starts around 7 to 14 days after full vaccination (depending on vaccine brand).
• Check your local guidance for when vaccine protection starts. Duration of protection is unknown and is still being assessed in ongoing clinical trials.
• Have a high level of suspicion of reported symptoms post-vaccination, and avoid dismissing complaints as vaccine-related until vaccine recipients are tested and true infection is ruled out.[346]

- Breakthrough infections are possible. Vaccinated people should continue to follow local public health recommendations.

- Breakthrough infections that have resulted in hospitalization or death, as well as mild or asymptomatic infections, have been reported in fully vaccinated people.[347] Vaccinated people should therefore be considered a possible source of transmission.[348] Vaccinated people are more likely to experience breakthrough infections more than 3 months after the second vaccine dose.[349]

- Breakthrough infections have been reported with the Omicron variant, including people who have received a booster dose.[350] While breakthrough infections with the Omicron variant are more frequent compared with the Delta variant, hospital admissions were less frequent with Omicron.[351]

- Risk factors for breakthrough infection after the first dose may include frailty in older adults ≥60 years, dementia, living in deprived areas, immune dysfunction, cancer (especially hematologic malignancies and those undergoing active cancer care), and obesity.[352] [353] [354] [355] [356] Older age, male sex, increasing number of comorbidities, hospitalization in the previous 4 weeks, high-risk occupation, care home residence, socioeconomic deprivation, and smoking history were all associated with an increased risk of hospitalization or death in patients with breakthrough infections after the first dose.[357] Prior infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be associated with a lower risk for breakthrough infection.[358]

- One small observational study in patients admitted to hospital with a positive test found that 46% of fully vaccinated people with breakthrough infection were asymptomatic, while 26% had severe or critical disease, 20% had moderate disease, and 7% had mild disease.[359] In another study, the rate of severe disease or death per 1000 person-days was 4.08 among those with breakthrough infections and 3.6 among unvaccinated matched controls with infection.[360]

- Emerging evidence indicates that fully vaccinated people with breakthrough infections have similar viral loads of the Delta variant compared with unvaccinated people, and are therefore equally likely to transmit the infection, including to fully vaccinated contacts.[361] [362] The secondary attack rates among household contacts exposed to fully vaccinated index cases was similar to household contacts exposed to unvaccinated index cases (25% for vaccinated versus 23% for unvaccinated).[363]

Vaccines: dose schedules

- The primary vaccination series consists of either a two-dose or one-dose schedule depending on the vaccine used (see table below).

- Dose intervals for the two-dose series may differ between countries depending on vaccine coverage rates and supply constraints.

- The WHO and the US Centers for Disease Control and Prevention recommend 3 weeks (Pfizer/BioNTech vaccine) or 4 weeks (Moderna vaccine) to 8 weeks between the first and second doses of mRNA vaccines. An interval of 8 weeks is preferred as this interval is associated with higher vaccine efficacy and a lower risk of myocarditis (e.g., in young men). However, there may be some groups who require quick protection (e.g., high-risk groups, settings of high transmission intensity).[338] [339] [364]

- Additional doses are recommended as part of the primary vaccination series for immunocompromised people.
The WHO recommends that the primary vaccination series for all vaccines should be extended to include an additional dose in moderately to severely immunocompromised people ages ≥5 years. The additional dose should be given at least 1 month and within 3 months after the primary series (or at the earliest opportunity if more than 3 months have elapsed). The most appropriate timing for the additional dose may vary depending on the epidemiologic setting and the timing and extent of the immunosuppressive therapy the patient is receiving. A homologous additional dose is standard practice, but alternative heterologous regimens for the additional dose may also be considered, taking into account current vaccine supply, vaccine supply projections, and other access considerations. The Pfizer/BioNTech vaccine is recommended in children ages 5 to 11 years.

In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) recommends an additional dose in severely immunocompromised people ages ≥5 years, at least 8 weeks after the second dose, with special attention paid to current or planned immunosuppressive therapies. Choice of vaccine depends on the person’s age and the vaccine used for the primary series. The Pfizer/BioNTech vaccine is preferred in those ages 5 to 17 years.

In the US, the Centers for Disease Control and Prevention recommends an additional dose in moderately or severely immunocompromised people ages ≥5 years (Pfizer/BioNTech vaccine) or ≥18 years (Moderna vaccine), at least 4 weeks after completion of the primary vaccination series. In those who receive a primary Janssen vaccine dose, a second (additional) dose using an mRNA vaccine is recommended at least 4 weeks after the first dose.

There are no vaccine efficacy studies following a third dose in immunocompromised people. Although there is no direct evidence that the ability to produce antibodies in these patients offers protection, it is expected that the extra dose increases protection, at least in some patients. The risk of adverse effects after an additional dose is not known and is being monitored.

Booster doses are recommended after the primary vaccination series.

The WHO recommends that the introduction of booster doses should be firmly evidence-driven and targeted to the population groups at highest risk of serious disease and those necessary to protect the health system. A booster dose is recommended for the highest priority-use groups 4 to 6 months after the completion of the primary series. Once high booster dose coverage has been achieved in these groups, a booster may be considered for other lower priority-use groups. If more than 6 months have elapsed since completion of the primary series, the booster dose should be given at the earliest opportunity. The need for booster doses in children ages 5 to 11 years has not yet been determined. A vaccination strategy based on repeated booster doses of the original vaccine composition is unlikely to be appropriate or sustainable.

In the UK, the JCVI recommends that all people ages ≥16 years should be offered a first booster dose at least 3 months after the completion of the primary course. Severely immunosuppressed people should be offered a booster dose with a minimum of 3 months between the third primary and booster dose. A booster should also be offered to people ages 12 to 15 years who are in a clinical risk group or who are a household contact of someone (of any age) who is immunosuppressed, or who are severely immunocompromised and who have had a third primary dose. Both the Pfizer/BioNTech and Moderna vaccines should be used with equal preference. Boosters in children ages 12 to 15 years who are not at high risk and in those ages 5 to 11 years will be reviewed in due course. Another (second) booster dose is recommended in adults ages ≥75 years, residents in care homes, and people ≥12 years who are immunosuppressed, around 6 months after the last dose, in March to May (Spring) 2022.

In the US, the Centers for Disease Control and Prevention recommends that all people ages ≥12 years should receive a first booster dose. Recipients of an mRNA primary series should receive a booster dose at least 5 months after completing their primary series (at least 3 months in people who are moderately or severely immunocompromised). Recipients of a Janssen primary series should receive a booster dose at least 2 months after completing their primary series. Any of the vaccines can be used for booster vaccination, regardless of the vaccine used for the primary series. However, an mRNA vaccine is preferred over the Janssen vaccine for booster vaccination, and only the Pfizer/BioNTech vaccine is recommended in adolescents.
Another (second) booster dose of an mRNA vaccine may be considered at least 4 months after the first booster dose in people ages ≥12 years who are moderately or severely immunocompromised, and all adults ages ≥50 years. People ages ≥18 years who are not moderately to severely immunocompromised and who received a Janssen vaccine for their primary series and booster dose may receive a second booster dose using an mRNA vaccine at least 4 months after the first Janssen vaccine booster dose. Booster doses of Pfizer/BioNTech and Janssen vaccines are the same as the primary series. However, the booster dose of the Moderna vaccine is half the dose used for the primary series. In moderately or severely immunocompromised people, the booster doses are the fourth or fifth doses as there are 3 doses in the primary series.[364]

- The European Centre for Disease Prevention and Control and the European Medicines Agency's COVID-19 task force have concluded that it is too early to consider using a second booster of mRNA vaccines in the general population as there is currently no clear evidence that vaccine protection against severe disease is waning substantially in adults with normal immune systems ages up to 79 years. However, both agencies agree that a second booster can be given to adults ≥80 years of age due to the higher risk of severe disease in this age group.
- Evidence for the benefit of a first booster dose is inferred through immunogenicity, and the overall level of certainty is very low for prevention of symptomatic disease, hospitalization, and death, as well as serious adverse events and reactogenicity.[375] In the ongoing, placebo-controlled, randomized, phase 3 trial, a booster dose administered a median of 10.8 months after the second dose provided 95.3% efficacy compared with two doses during a median follow-up of 2.5 months. No new safety signals were identified.[376] Observational data to support the safety and efficacy of booster doses are emerging, but their follow-up periods are too short to assess long-term effectiveness, and the number of trial participants is small.[377][378][379][380][381][382][383][384] The studies also focus on plasma neutralizing antibodies and don’t take into account the protection provided by cellular immunity. More data are needed to understand the potential impact of booster vaccination on the duration of protection against severe disease, mild disease, infection, and transmission, particularly in the context of emerging variants.[370]
- Evidence for the benefit of a second booster dose is emerging and comes largely from Israel.[385][386][387] Approval of a second booster dose by the US Food and Drug Administration was based on a summary of safety surveillance data provided to the agency by the Ministry of Health of Israel.[388]
- There are currently no data available on the efficacy of booster doses for inactivated whole-virus vaccines.[389]

* Heterologous vaccination schedules may be recommended in some countries.

- The WHO recommends that homologous schedules should be considered standard practice. However, a flexible approach is supported, and two heterologous doses of any authorized vaccine may be used to be a complete primary series. Heterologous vaccination should only be implemented with careful consideration of current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used. The relative risks and benefits of homologous versus heterologous primary and booster doses will continue to be reviewed.[390]
- Cohort studies have found that heterologous vaccination schedules induce a robust humoral and cellular immune response after a second dose of an mRNA vaccine in people primed with the AstraZeneca vaccine 8 to 12 weeks earlier, and were associated with an acceptable and manageable reactogenicity profile.[391][392][393][394][395] However, some studies have found an increase in transient systemic reactogenicity after the boost dose of an mRNA vaccine in heterologous vaccine schedules in comparison to homologous vaccine schedules in participants ages 50 years and older.[396][397][398] The difference between studies may be explained, in part, by the difference in administration intervals used between the studies (i.e., 28 days versus 8-12 weeks).
- The European Medicines Agency and the European Centre for Disease Prevention and Control have published guidance on when to use heterologous schedules for the primary vaccination series and booster doses.[399]
• Consider administering COVID-19 vaccines and influenza vaccines together.

  • The WHO recommends that coadministration of any dose of a COVID-19 vaccine with an inactivated seasonal influenza vaccine is acceptable and may be considered during the same visit. Only limited evidence exists to support this recommendation, but available evidence does not show increased adverse events. The WHO recommends using the contralateral limb for injection when the two vaccines are administered during the same visit to minimize any perceived risk, and monitoring for adverse effects after. No coadministration data are available for other live or inactivated vaccines.[400]

  • In the UK, the JCVI advises that COVID-19 vaccines and influenza vaccines may be administered together where operationally practical, although there are a lack of data to support this.[401]

  • In the US, the National Institutes of Health recommends deferring influenza vaccination in patients with symptomatic COVID-19 until the patient has completed their isolation period and they are no longer moderately or severely ill. It also recommends deferring influenza vaccination in patients with asymptomatic or mild COVID-19 until the patient has completed their isolation period.[19]

  • A multicenter randomized controlled phase 4 trial found that concomitant COVID-19 and influenza vaccine administration raised no safety concerns, most systemic reactions were mild or moderate, and the immune response was not adversely affected.[402] Similar results have been reported in an ongoing phase 2, open-label trial in older adults.[403]

• Consult your local guidelines for detailed information on dose schedules.

  • [CDC: interim clinical considerations for use of COVID-19 vaccines currently approved or authorized in the United States] (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html)

### Management

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<tr>
<th>Vaccine</th>
<th>Primary Series</th>
<th>Booster Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/BioNTech (orange cap)</td>
<td>5-11 years: 0.2 mL (10 mcg) IM; second dose 3 weeks later; third dose 4 weeks later in moderately or severely immunocompromised</td>
<td>Not currently recommended in this age group</td>
</tr>
<tr>
<td>Pfizer/BioNTech (purple or grey cap)</td>
<td>≥12 years: 0.3 mL (30 mcg) IM; second dose 3-8 weeks* later; third dose 4 weeks later in moderately or severely immunocompromised</td>
<td>≥12 years: 0.3 mL (30 mcg) IM at least 5 months after primary series (3 months in moderately or severely immunocompromised); a second booster may be offered 4 months after the first booster**</td>
</tr>
<tr>
<td>Moderna (red cap)</td>
<td>≥18 years: 0.5 mL (100 mcg) IM; second dose 4-8 weeks* later; third dose 4 weeks later in moderately or severely immunocompromised</td>
<td>Booster series: ≥18 years: 0.25 mL (50 mcg) IM at least 5 months after primary series (3 months in moderately or severely immunocompromised); a second booster may be offered 4 months after the first booster**</td>
</tr>
<tr>
<td>Janssen (blue cap)</td>
<td>≥18 years: 0.5 mL IM as a single dose; second dose of an mRNA vaccine 4 weeks later in moderately or severely immunocompromised (use is limited to certain people)</td>
<td>≥18 years: 0.5 mL IM at least 2 months after primary series; a second booster may be offered 4 months after the first booster**</td>
</tr>
</tbody>
</table>

*Dose information for COVID-19 vaccines currently approved or authorized in the US based on guidelines from the Centers for Disease Control and Prevention. *An 8-week interval may be optimal for some people (e.g., males ages 12 to 39 years due to risk of myocarditis associated with mRNA vaccines). **A second booster may be considered in some people. [338] [339] [340] [341] [342] [343] [344] In addition to this, people who have had thrombosis with thrombocytopenia syndrome following the first dose of the AstraZeneca vaccine should not receive a second dose of the vaccine. [340]

**Vaccines: contraindications**

- A history of anaphylaxis or hypersensitivity to any component of the vaccine is a contraindication to vaccination. If anaphylaxis occurs after the first dose, a second dose of the vaccine should not be administered. In addition to this, people who have had thrombosis with thrombocytopenia syndrome following the first dose of the AstraZeneca vaccine should not receive a second dose of the vaccine.

- Other contraindications may apply to specific vaccines in different countries. Consult your local guidance for more information.
• Use caution in people receiving anticoagulant therapy or those with bleeding disorders due to the risk of bleeding or bruising with intramuscular injections.

• In the US, the Janssen vaccine has been limited to use in certain people. The Food and Drug Administration has limited the authorized use of the Janssen vaccine to individuals ≥18 years of age for whom other authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, and to individuals ≥18 years of age who elect to receive the Janssen vaccine because they would otherwise not receive a COVID-19 vaccine. The agency has determined that the risk of vaccine-induced immune thrombocytopenia and thrombosis (see Vaccines: adverse events below) warrants limiting the authorized use of the vaccine.[404]

Vaccines: adverse events

• Myocarditis and pericarditis

  • Myocarditis or pericarditis may occur following vaccination with mRNA vaccines.[405] It has been postulated that mRNA vaccines may increase inflammation on the endothelium and T-cell infiltration of cardiac muscle, but further research is required.[406] Cases have also been reported with adenovirus vector vaccines, albeit more rarely.[407]

  • Estimates of incidence vary. In the UK, 18 cases of myocarditis per million doses have been reported with the Moderna vaccine and 10 cases per million doses with the Pfizer/BioNTech vaccine across all ranges after first, second, and third doses, according to the Yellow Card reporting system (as of 20 April 2022). The incidence of pericarditis is slightly lower (10 cases per million doses for Moderna, and 7 cases per million doses for Pfizer/BioNTech). Rates of myocarditis and pericarditis are highest in the 18-to-29-years age group (29 cases per million doses after the second dose of the Pfizer/BioNTech vaccine, and 69 cases per million doses after the second dose of the Moderna vaccine). There appears to be an increased risk after the third dose (booster), but data is still emerging and the risk may be lower than after the second dose.[408] [409] In the US, monitoring by the Vaccine Adverse Event Reporting System (VAERS) detected 70.7 cases of myocarditis per million doses in males ages 12 to 15 years after the second dose, 105.9 cases per million doses in males ages 16 to 17 years, and 52.4 to 56.3 cases per million doses in males ages 18 to 24 years (as of 30 September 2021).[410] Estimates are based on data from passive surveillance systems so the true number of cases may be higher.

  • Cases occur predominantly in adolescents and young adults (median age of onset 21 years), more often in males than in females, more often following the second dose, and typically within 3 days after vaccination (up to 25 days).[411] In a cohort study of 23.1 million residents ages ≥12 years across four Nordic countries, the risk of myocarditis was higher within 28 days of vaccination with both mRNA vaccines compared with being unvaccinated. The risk was highest within the first 7 days of being vaccinated, was increased for all combinations of mRNA vaccines, and was more pronounced after the second dose (with young males ages 16-24 years having the highest risk).[412]

  • Consider the diagnosis in children, adolescents, or adults with new-onset and unexplained significant chest pain, tachycardia or tachypnea, dyspnea, palpitations, dizziness or syncope, or general clinical concern, within 10 days of vaccination. Order a 12-lead electrocardiogram, inflammatory blood markers, and troponin. If any of these investigations are abnormal, discuss the management plan with the cardiology team.[413]


  • The short-term clinical course appears to be mild in most patients, but the long-term risks remain unknown.[414]

  • In the UK, the UK Health Security Agency recommends that if there is no evidence of ongoing myocarditis at the 8-week follow-up, people may be offered vaccination with the Pfizer/BioNTech vaccine from 12 weeks after their last dose if further doses are due. An individual risk-benefit assessment is recommended if there is evidence of ongoing effects of acute or subacute myocarditis at the 8-week follow-up.[413]
• In the US, the Centers for Disease Control and Prevention recommends that people with a history of myocarditis or pericarditis after a dose of an mRNA vaccine should generally avoid a subsequent dose of any COVID-19 vaccine. If the decision is made to administer a subsequent dose after a risk assessment is made, the person should wait until at least after the episode has resolved.[364]

• Guillain-Barre syndrome may occur following vaccination with adenovirus vector vaccines. Cases have also been reported with mRNA vaccines, albeit more rarely.[415] [416]

• Estimates of incidence vary. In the UK, 495 cases of Guillain-Barre syndrome and 29 cases of Miller Fisher syndrome have been reported with the AstraZeneca vaccine, 102 cases of Guillain-Barre syndrome and 5 cases of Miller Fisher syndrome have been reported with the Pfizer/BioNTech vaccine, and 17 cases of Guillain-Barre syndrome have been reported with the Moderna vaccine (as of 20 April 2022).[408] In the US, monitoring by VAERS detected 1 case of Guillain-Barre syndrome per 100,000 doses of the Janssen vaccine (as of 24 July 2021). The median time to onset following vaccination was 13 days (range 10-42 days), and 93% of cases were serious.[417]

• Vaccine-induced immune thrombocytopenia and thrombosis (VITT)

• VITT may occur following vaccination with adenovirus vector vaccines.[418] Cases have also been reported with mRNA vaccines, albeit more rarely.[419]

• Estimates of incidence vary. In the UK, 15.7 cases per million doses have been reported after first or unknown doses of the AstraZeneca vaccine (21.4 per million in people ages 18-49 years), and 2.1 cases per million doses have been reported after the second dose, with a case fatality rate of 18% (as of 20 April 2022).[408] In the US, the overall risk with the Janssen vaccine has currently been estimated to be 3.83 cases per million people who receive the vaccine, with the reporting rate highest among women ages 30 to 39 years (10.6 cases per million doses) and 40 to 49 years (9.02 cases per million doses), with a case fatality rate of 15%.[420]

• Some countries have implemented age-related prescribing restrictions for adenovirus vector vaccines. In the UK, the JCVI advises that it is preferable for adults ages <40 years without underlying health conditions to receive an alternative to the AstraZeneca vaccine if possible.[421] In the US, the Janssen vaccine has been limited to use in certain people due to the risk of VITT (see Vaccines: contraindications above).[404] Consult your local guidance.

• The World Health Organization recommends that people who have had VITT following the first dose of the AstraZeneca vaccine should not receive a second dose of the same vaccine.[340] A small cohort study found that none of the 40 patients who experienced VITT after their first dose of the AstraZeneca vaccine had any relapse of symptoms or severe adverse reactions after receiving their second dose, regardless of the vaccine received. However, the majority of people received the Pfizer/BioNTech vaccine as their second dose.[422]

• Use caution in people with a history of heparin-induced thrombocytopenia or cerebrovascular venous and sinus thrombosis. The US Centers for Disease Control and Prevention recommends that people with a history of an episode of an immune-mediated syndrome characterized by thrombosis and thrombocytopenia, such as heparin-induced thrombocytopenia, should be offered an mRNA vaccine instead of an adenovirus vector vaccine.[364]

• There is a link to rare cases of venous thromboembolism that is distinct from VITT, and cerebral venous sinus thrombosis without thrombocytopenia with adenovirus vector vaccines.[423] [424] A retrospective cohort study found that vaccination with the AstraZeneca vaccine was associated with a small excess risk for deep vein thrombosis.[425]

• See the Complications section for more information on VITT, including diagnosis and management.

• Anaphylaxis

• Severe allergic reactions, including anaphylaxis, may occur after vaccination. Reactions may be due to the presence of lipid pegylated ethylene glycol (PEG), or PEG derivatives such as polysorbates.[426]
• Globally, the pooled incidence of post-vaccination anaphylaxis has been estimated to be between 5.58 to 7.91 cases per million doses based on available data, and depends on the vaccine used. However, rates as high as 32 per million doses (Moderna) and 38 per million doses (Pfizer/BioNTech) have been reported.

• A history of anaphylaxis to any component of the vaccine is a contraindication to vaccination. People who have an anaphylactic reaction following the first dose of the vaccine should not receive a second dose of the same vaccine. Observe people for 15 to 30 minutes after vaccination in healthcare settings where anaphylaxis can be immediately treated.[338] [339] [340] [341] [342] [343] [344] Some countries have removed the requirement for the observation period following vaccination in certain people. Consult local guidelines for recommendations on vaccinating people with a history of allergies or anaphylaxis.

• A systematic review and meta-analysis of case studies and case reports found that the risk of immediate allergic reactions, including anaphylaxis, associated with a second dose of an mRNA vaccine was low among people who experienced an immediate allergic reaction to the first dose.[430]

• Immune thrombocytopenia

• Immune thrombocytopenia may occur following vaccination with adenovirus vector vaccines. Use caution in people with a history of a thrombocytopenic disorder. People with a history of a thrombocytopenic disorder should have their platelets monitored for the first 4 weeks following vaccination.[423]

• Estimates of incidence vary. In the UK, 4 cases per million doses have been reported with the AstraZeneca vaccine (as of 20 April 2022). Approximately 10% to 20% of cases had a history of immune thrombocytopenia or an underlying condition known to be associated with immune thrombocytopenia.[408]

• Transverse myelitis

• Transverse myelitis may occur rarely following vaccination.[431] Signs and symptoms include muscle weakness, localized or radiating back pain, bladder and bowel symptoms, and changes in sensation. Evidence suggests a possible association between transverse myelitis and the AstraZeneca vaccine.[408] Cases have also been reported with mRNA vaccines, albeit more rarely.[432]

• Estimates of incidence vary. In the UK, 122 cases of transverse myelitis have been reported with the AstraZeneca vaccine, 37 cases with the Pfizer/BioNTech vaccine, and 4 cases with the Moderna vaccine (as of 20 April 2022).[408]

• People who have an episode of transverse myelitis following the first dose of the AstraZeneca vaccine should not receive a second dose of this vaccine.[408]

• Other adverse events and safety signals

• See table below for a complete list of adverse events included in the manufacturer’s prescribing information. Other reported adverse events (e.g., case reports) and safety signals are detailed below; however, a causal link may not have been confirmed, and this list is not exhaustive.

• Cardiovascular/pulmonary: myocardial infarction, Takotsubo cardiomyopathy, isolated tachycardia.[433] An epidemiologic study suggests a slightly increased risk for myocardial infarction and pulmonary embolism after adenovirus vector vaccines, and the European Medicines Agency is currently assessing this risk.[434] [435]

• Dermatologic: Stevens-Johnson syndrome, cutaneous vasculitis, erythematous and indurated skin reactions.[436] [437] [438]

• Endocrine: Graves disease, subacute thyroiditis, menstrual disorders.[408] [439] [440] [441]

• Gastrointestinal: acute necrotizing pancreatitis, autoimmune hepatitis (although the European Medicines Agency has ruled out a causal link at this stage).[442] [443] [444] [445] [446]

• Hematologic: acquired hemophilia A.[447]

• Neurologic: varicella zoster virus reactivation, demyelinating diseases, neuropathy, hemorrhagic stroke, myasthenic disorders, encephalopathy/encephalitis, acute disseminated encephalomyelitis, acute demyelinating polyneuropathy, new-onset multiple sclerosis,
neuromyelitis optica spectrum disorder, sensorineural hearing loss.[415] [448] [449] [450] [451] [452] [453] [454]

- Renal: minimal change disease, IgA nephropathy, vasculitis, membranous nephropathy, scleroderma renal crisis.[455]
- Rheumatologic: rheumatoid arthritis, systemic lupus erythematosus, inflammatory myositis, adult-onset Still’s disease.[443] [456] [457]
- Fatal adverse events have been reported rarely post vaccination, and have been confirmed in postmortem studies.[458]

* Report all suspected adverse events after vaccination via your local reporting system. This is mandatory in some countries. Surveillance of adverse events is extremely important, and may reveal additional, less frequent serious adverse events not detected in clinical trials. The mRNA vaccines have not been authorized for use in humans previously, so there is no long-term safety and efficacy data available for these types of vaccines.

- US: [Vaccine Adverse Event Reporting System (VAERS)](https://vaers.hhs.gov)
- International: [WHO: Adverse Event Following Immunization (AEFI) form](http://investigation.gvsi-aefi-tools.org/#step-1)
### Adverse effects associated with vaccines authorized or approved in the US.

Information is taken from the US prescribing information. Last updated: 12 May 2022

BMJ Best Practice editorial team; compiled using data from the US product information

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<tr>
<th>Vaccines: special patient populations</th>
</tr>
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<tbody>
<tr>
<td><strong>Pregnancy</strong></td>
</tr>
<tr>
<td>- The WHO recommends offering vaccination to all pregnant women. The WHO does not recommend pregnancy testing prior to vaccination, or delaying pregnancy or terminating a pregnancy because of vaccination.[338] [339] [340] [341]</td>
</tr>
<tr>
<td>- In the UK, the JCVI and the Royal College of Obstetricians and Gynaecologists recommend that vaccination should be offered to pregnant women at the same time as the rest of the population, based on age and clinical risk (preferably with an mRNA vaccine).[459] [460]</td>
</tr>
<tr>
<td>- In the US, the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommend that all pregnant women, or women who are thinking about or trying to become pregnant, should be vaccinated.[364] [461]</td>
</tr>
<tr>
<td>- There are limited safety and efficacy data available in pregnant women.[462] Observational studies have not identified any safety signals as yet.[463] [464] [465] [466] [467] [468] However, these data have limitations, and continued monitoring is needed to further assess the risk.</td>
</tr>
</tbody>
</table>

* Breastfeeding
• The WHO recommends offering vaccination to all breastfeeding women. The WHO does not recommend discontinuing breastfeeding because of vaccination.[338] [339] [340] [341]
• In the UK, the JCVI and the Royal College of Obstetricians and Gynaecologists recommend that vaccination should be offered to breastfeeding women and there is no need to stop breastfeeding.[459] [460]
• In the US, the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommend that all breastfeeding women should be vaccinated.[364] [461]
• There are limited safety and efficacy data available in breastfeeding women. Studies have found robust secretion of SARS-CoV-2 specific immunoglobulin A (IgA) and IgG antibodies in breast milk after vaccination.[469] However, it is unclear how long antibodies persist in the breast milk after vaccination, and their impact on the prevention of infection in infants is also unclear. Vaccine-associated mRNA was not detected in 13 milk samples collected 4 to 48 hours after vaccination from 7 breastfeeding individuals.[470] However, further research is required.

• Children and adolescents (12 to 17 years of age)
  • The WHO recommends that children and adolescents ages 12 to 17 years of age with comorbidities that put them at higher risk of serious disease should be offered vaccination with the Pfizer/BioNTech or Moderna vaccines. The WHO recommends that countries consider vaccination in this age group only when high vaccine coverage (primary series and boosters) has been achieved in the higher priority-use groups.[338] [339]
  • The Pfizer/BioNTech and Moderna vaccines have been authorized for use in children ages ≥12 years and adolescents in some countries. Authorization was based on an ongoing randomized, placebo-controlled clinical trial of over 2000 participants that reported 100% efficacy from 7 days after the second dose.[471] Due to the limited number of children included in the study, the trial could not have detected rare adverse effects such as myocarditis. However, safety monitoring of VAERS noted over 9000 reports of adverse events post-vaccination in adolescents ages 12 to 17 years (as of 16 July 2021), 9.3% of which were for serious adverse events including myocarditis (4.3%).[472]
  • The Pfizer/BioNTech vaccine may be preferred over the Moderna vaccine in this age group due to a lower reported rate of myocarditis/pericarditis.[367] The US Food and Drug Administration has put an application for the authorization of the Moderna vaccine in this age group on hold while it investigates the risk.[473]
  • In the UK, the JCVI recommends that all children ages 12 to 15 years should be offered their second dose of the Pfizer/BioNTech vaccine at a minimum of 12 weeks after the first dose. The interval may be reduced to at least 8 weeks if the emerging epidemiologic data support this. Those ages 16 to 17 years may also be offered their second dose with an interval of at least 8 weeks.[372]
  • In the US, the the Centers for Disease Control and Prevention recommends vaccination with the Pfizer/BioNTech vaccine in all children and adolescents ages ≥12 years (primary vaccination series and booster doses). The Moderna and Janssen vaccines are not currently recommended in this age group.[364]
  • Available evidence suggests that the safety and efficacy of vaccines are acceptable in this age group. Older children and adolescents were at significantly increased risk of adverse reactions after vaccination compared with younger children. There is a need for additional multicenter, large-sample studies and long-term follow-up data.[474]
  • Consult your local guidance as recommendations on vaccinating children and adolescents vary.

• Children (5 to 11 years of age)
  • The WHO recommends that children ages 5 to 11 years of age with comorbidities that put them at higher risk of serious disease should be offered vaccination with the Pfizer/BioNTech vaccine. The WHO recommends that countries consider vaccination in this age group only when high vaccine coverage (primary series and boosters) has been achieved in the higher priority-use groups.[338]
  • The Pfizer/BioNTech vaccine has been authorized for use in children ages 5 to 11 years in some countries. Authorization was based on an ongoing randomized placebo-controlled clinical trial of
approximately 4700 children 5 to 11 years of age that reported 90.7% efficacy from 7 days after the second dose. Safety analysis was based on only 1444 participants.[475] Due to the limited number of children included in the study, the trial could not have detected rare adverse effects such as myocarditis. However, preliminary real world data has not picked up an increased risk of myocarditis in this age group as yet.[476]  
• In the UK, the JCVI recommends that children ages 5 to 11 years who are in a clinical risk group, or who are a household contact of someone (of any age) who is immunosuppressed, should be offered a primary course of the Pfizer/BioNTech vaccine.[373] Although this age group is generally at very low risk of serious illness from the virus, the committee has also advised a nonurgent offer of vaccination to all children ages 5 to 11 years of age.[477] The UK’s Medicines and Healthcare products Regulatory Agency has approved the Moderna vaccine for children ages 6 to 11 years.[478]  
• In the US, the Centers for Disease Control and Prevention recommends a primary course of vaccination with the Pfizer/BioNTech vaccine in all children ages 5 to 11 years (primary vaccination series only; booster doses are not currently recommended in this age group). The Moderna and Janssen vaccines are not currently recommended in this age group.[364]  
• Use caution when administering the vaccine to this age group. A lower dose of the Pfizer/BioNTech vaccine is recommended, and the most common adverse events in this age group were related to administration errors.[476] Vaccine vials may have different colored caps to help prevent dose administration errors.  
• Available evidence suggests that the safety and efficacy of vaccines are acceptable in this age group. There is a need for additional multicenter, large-sample studies and long-term follow-up data.[474]  
• Consult your local guidance as recommendations on vaccinating children vary.

• Current or previous SARS-CoV-2 infection

• Delayed vaccination is recommended in people with current acute COVID-19 or any other acute febrile illness (until they have recovered from the acute illness and are afebrile and the criteria for discontinuation of isolation have been met), and people who previously received passive antibody therapy for COVID-19 (for at least 90 days). Delayed vaccination may also be considered in people who have had confirmed SARS-CoV-2 infection in the preceding 3 to 6 months (until near the end of this period).[338] [339] [340] [341]  
• Emerging data indicate that symptomatic reinfection may occur sooner in settings where variants of concern are circulating. In these settings, earlier immunization after infection may be advisable (e.g., within 90 days following natural infection).[338]  
• Emerging evidence suggests that one dose of the vaccine may be sufficient for people who have already been infected with SARS-CoV-2.[479] [480] [481]  
• A higher rate of adverse effects has been reported after the first dose of the vaccine in people with a history of SARS-CoV-2 infection compared with participants who had not previously been infected, but not after the second dose.[482]  

• Immunocompromised

• Seroconversion rates were significantly lower in immunocompromised people, especially solid organ transplant recipients, but increased after the second dose. However, seroconversion remained severely reduced in solid organ transplant recipients even after a second dose compared with the general population.[483] Approximately 20% to 40% of solid organ transplant recipients did not mount an antibody response despite receiving multiple doses of mRNA vaccines.[484]  

• Autoimmune disease

• Data suggests that vaccine efficacy may be lower in patients with autoimmune disease.[485] [486] [487] It is uncertain whether vaccines may cause an exacerbation of preexisting autoimmune diseases; however, there are case reports of new autoimmune conditions or flares of existing autoimmune conditions post vaccination.[488] [489] [490] [491] Further research is needed to understand vaccine efficacy among this group.  

• Malignancy
• Data suggests that vaccine efficacy may be lower in cancer patients compared with the general population. Antibody response was lower in hematologic malignancies compared with solid tumors. Antibody response was also lower for allogeneic and autologous hematopoietic stem cell transplant recipients, and those receiving active treatment. The response varied depending on the treatment; lower responses were reported for anti-CD20 therapies, Bruton kinase inhibitors, venetoclax, ruxolitinib, and chimeric antigen receptor T-cell therapy.[492] Further research is needed to understand vaccine efficacy among this group.

Vaccines: efficacy

• Initial authorization of vaccines was based on interim analyses of ongoing phase 3 clinical trials with a median follow-up of 2 months. Overall initial reported vaccine efficacy for preventing symptomatic infection was reported as 95% (Pfizer/BioNTech), 94.1% (Moderna), 74% (AstraZeneca), and 66.9% (Janssen).[493] [494] [495] [496]

• Observational evidence from the initial global vaccine rollout suggested real-world efficacy in reducing the rate of symptomatic or asymptomatic infection, disease severity, hospitalization, death, and possibly even reinfection. However, evidence indicates a minimal to modest reduction of vaccine protection against severe disease over the 6 months after the primary series, while waning efficacy against all clinical disease and infection is more pronounced. Vaccine efficacy against severe disease decreased by about 8% over a 6-month period in all age groups (10% in those ages >50 years), and vaccine efficacy against symptomatic disease decreased by 32% in those ages >50 years.[370]

• Vaccine efficacy varies depending on the SARS-CoV-2 variant. Efficacy is highest for the Alpha variant, with lower efficacy reported for Beta and Gamma variants.[497] There is a lack of evidence for the Delta variant; however, vaccine efficacy (in terms of testing positive and onwards transmission) for the Delta variant appears to be reduced relative to other variants.[498] [499] [500] See the Classification section for evolving information on vaccine efficacy against the Omicron variant.

• Observational studies suggest that people who receive at least one dose of the Pfizer/BioNTech vaccine after prior SARS-CoV-2 infection may have a decreased risk of recurrent/breakthrough infection compared with those who remain unvaccinated; however, these studies have many limitations.[501] [502] [503]

• Previous trials of coronavirus vaccines identified cellular immunopathology and antibody-dependent enhancement as potential safety issues.[504] [505]

• Available data do not indicate a risk of vaccine-enhanced disease with the mRNA vaccines; however, data are limited and the risk over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further.[493] [494] The possibility of antibody-dependent enhancement in people receiving vaccines based on the original virus strain spike sequence who are then exposed to the Delta variant has not been studied.[506]

Monoclonal antibodies: pre-exposure prophylaxis

• Tixagevimab/cilgavimab is authorized in some countries for pre-exposure prophylaxis.

• Tixagevimab/cilgavimab is a long-acting, neutralizing monoclonal antibody combination with activity against SARS-CoV-2. It is designed to attach to the spike protein of the virus at two different sites.

• It is authorized for use in the US, the UK, and Europe.[507] [508] [509]

• Guideline recommendations for the use of tixagevimab/cilgavimab vary. Consult your local guidance.

• In the US, the National Institutes of Health guidelines panel recommends tixagevimab/cilgavimab for pre-exposure prophylaxis in children ages ≥12 years (weighing ≥40 kg) and adults who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, AND who are moderately to severely immunocompromised and may have an inadequate immune response to vaccination, or are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe reactions. This included people with advanced or untreated HIV infection.[19]
• The Infectious Diseases Society of America supports the use of tixagevimab/cilgavimab for pre-exposure prophylaxis.\[510\]

• Consult your local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this treatment.

  • Tixagevimab/cilgavimab is given as a single dose administered as two separate consecutive intramuscular injections.
  • Serious cardiac adverse events were reported infrequently in the clinical trial; however, it is unknown whether these events were caused by the drug.

• Circulating SARS-CoV-2 variants may be associated with resistance to monoclonal antibodies.

  • In vitro data show that the Omicron BA.1 and BA.1.1 subvariants have decreased susceptibility to tixagevimab/cilgavimab.\[19\] However, according to the manufacturer, in vivo data suggests that tixagevimab/cilgavimab retains neutralizing activity against Omicron variants (including the BA.2 subvariant).\[511\]
  • Dose recommendations may depend on the local circulating variant and whether the patient has had the treatment previously.
  • Consult local guidance for details regarding specific variants and resistance.

• Evidence is limited.

  • In an ongoing multicenter, double-blind, parallel-group, randomized, placebo-controlled trial, tixagevimab/cilgavimab reduced the risk of developing symptomatic disease by 76.7% (relative risk reduction) compared with placebo at the primary analysis (median 83 days after administration), with an 82.8% relative risk reduction reported at the median 6-month follow-up. All cases of severe or critical disease were reported in the placebo group. The most common adverse event was injection-site reactions.\[512\]
  • A small cohort study found that pre-exposure administration of tixagevimab/cilgavimab was associated with a lower risk of infection in severely immunocompromised patients with immune-mediated inflammatory diseases who were fully vaccinated. However, due to the limitations of the study, these results should be interpreted with caution.\[513\]

Infection prevention and control for healthcare professionals

• Consult local infection prevention and control protocols; only basic principles from the World Health Organization (WHO) guidelines are detailed here.\[514\] \[515\]

• Screen all people, including patients, visitors, and others entering the facility, for COVID-19 at the first point of contact with the health facility to allow for early recognition.

• Immediately isolate all suspected or confirmed cases in a well-ventilated area that is separate from other patients. Place patients in adequately ventilated single rooms if possible. When single rooms are not available, place all cases together in the same adequately ventilated room and ensure there is at least 3 feet (1 meter) between patients.

• Implement standard precautions at all times:

  • Practice hand and respiratory hygiene
  • Give patients a medical mask to wear
  • Wear appropriate personal protective equipment
  • Practice safe waste management and environmental cleaning.

• Implement additional contact and droplet precautions before entering a room where suspected or confirmed cases are admitted.
• A respirator or medical mask should be worn along with other personal protective equipment (i.e., gown, gloves, eye protection) before entering a room with a suspected or confirmed case.

• A respirator should be worn in the following situations: in care settings where ventilation is known to be poor or cannot be assessed, or the ventilation system is not properly maintained; based on the worker’s values and preferences and on their perception of what offers the highest protection possible to prevent infection.

• Appropriate mask fitting should always be ensured, as should compliance with appropriate use of personal protective equipment and other precautions.

• Universal masking is strongly recommended in health facilities in areas of known or suspected community or cluster transmission.

• Implement airborne precautions when performing aerosol-generating procedures, including placing patients in a negative pressure room and wearing a particular respirator.

• A respirator should always be worn along with other personal protective equipment while performing aerosol-generating procedures, and in settings where these procedures are regularly performed on patients with suspected or confirmed disease (e.g., intensive care units, emergency departments).

• Some countries and organizations recommend airborne precautions for any situation involving the care of a COVID-19 patient.

• All specimens collected for laboratory investigations should be regarded as potentially infectious.

• Appropriate personal protective equipment gives healthcare workers a high level of protection.

• A cross-sectional study of 420 healthcare workers deployed to Wuhan with appropriate personal protective equipment tested negative for SARS-CoV-2 on molecular and serologic testing when they returned home, despite all participants having direct contact with COVID-19 patients and performing at least one aerosol-generating procedure.[516]

• Standard surgical masks are as effective as respirator masks for preventing infection of healthcare workers in outbreaks of viral respiratory illnesses such as influenza, but it is unknown whether this applies to COVID-19.[517]

• Avoid in-person assessment of patients with suspected COVID-19 in primary care when possible to avoid infection. Most patients can be managed remotely by telephone or video consultations.[518]

• Detailed infection prevention and control guidance is available:


Infection prevention and control for the general public

• Public health recommendations vary between countries and you should consult your local guidance.

• It is generally recommended that people stay at least 3 to 6 feet (1-2 meters) away from others (recommendations vary between countries), wash their hands often with soap and water (or hand sanitizer that contains at least 60% alcohol), cover coughs and sneezes, wear a mask (see Face masks below), avoid crowds and poorly ventilated spaces, clean and disinfect high
Coronavirus disease 2019 (COVID-19)

Management

- Countries may sometimes implement nonpharmaceutical interventions in order to reduce and delay viral transmission (e.g., social distancing, city lockdowns, stay-at-home orders, curfews, nonessential business closures, bans on gatherings, school and university closures, remote working, quarantine of exposed people).
  - Implementing any nonpharmaceutical interventions was associated with a significant reduction in case growth when comparing countries with more restrictive nonpharmaceutical interventions to countries with less restrictive nonpharmaceutical interventions. However, there was no clear, significant beneficial effect of more restrictive nonpharmaceutical interventions compared with less restrictive nonpharmaceutical interventions in any of the countries studied.
  - Negative consequences of community-based mass quarantine include psychological distress, food insecurity, economic challenges, diminished healthcare access, heightened communication inequalities, alternative delivery of education, and gender-based violence.
- Some countries have published guidance to support the next stage of the pandemic, living with COVID-19. This new phase focuses on protecting those who are most at risk from the virus. Consult your local guidance.
- The following guidance has been published in the UK:
  - [UKHSA: people with symptoms of a respiratory infection including COVID-19](https://www.gov.uk/guidance/people-with-symptoms-of-a-respiratory-infection-including-covid-19)
  - [UKHSA: guidance for people whose immune system means they are at higher risk](https://www.gov.uk/government/publications/covid-19-guidance-for-people-whose-immune-system-means-they-are-at-higher-risk)

Face masks

- Public health recommendations on wearing face masks vary between countries and you should consult your local guidance. Many countries have ended mask mandates, except in certain high-risk situations.
- The WHO recommends wearing a mask, regardless of vaccination status or history of prior infection, in settings where there is community or cluster transmission when interacting with nonhousehold members in the following circumstances:
  - Indoor settings where ventilation is poor or cannot be assessed, regardless of whether physical distancing of at least 3 feet (1 meter) can be maintained
  - Indoor settings with adequate ventilation if physical distancing cannot be maintained
  - Outdoor settings if physical distancing cannot be maintained
  - For people who are at higher risk of severe complications from infection, if physical distancing cannot be maintained in any setting.
- Masks are not recommended:
  - During vigorous-intensity physical activity
  - In children ages <5 years for source control (a risk-based approach should be applied to children ages 6-11 years)
In children with severe cognitive or respiratory impairments, developmental disorders, disabilities, or other specific health conditions who experience difficulties wearing a mask or have health conditions that interfere with mask-wearing.

There is no high-quality or direct scientific evidence to support the widespread use of masks by healthy people in the community setting. Data on effectiveness is based on limited and inconsistent observational and epidemiologic studies.

The only randomized controlled trial to investigate the efficacy of masks in the community found that the recommendation to wear surgical masks when outside the home did not reduce infection compared with a no mask recommendation. However, the study did not assess whether masks could decrease disease transmission from mask wearers to others (source control). Evidence from randomized controlled trials for other respiratory viral illnesses shows no significant benefit of masks in limiting transmission but is of poor-quality and not SARS-CoV-2-specific.

A Cochrane review found that wearing a mask may make little to no difference in how many people caught influenza-like illnesses. However, this was based on low-certainty evidence, and does not include results of studies from the current pandemic.

A living rapid review found that the evidence for mask effectiveness for respiratory tract infection prevention is stronger in healthcare settings compared with community settings; however, direct evidence on comparative effectiveness in SARS-CoV-2 infection is insufficient. The strength of evidence for any mask use versus nonuse in community settings is low-moderate.

Cloth masks have limited efficacy in preventing viral transmission compared with medical-grade masks and the efficacy is dependent on numerous factors (e.g., material type, number of layers, fitting, moisture level), and may result in increased risk of infection.

There are harms and disadvantages of wearing masks including headache, breathing difficulties, facial skin lesions, irritant dermatitis, worsening acne, difficulty wearing masks by certain members of the population (e.g., children, people with learning disabilities, mental illness or cognitive impairment, asthma, chronic respiratory or breathing problems, facial trauma or recent oral maxillofacial surgery, living in hot and humid environments), psychological issues, difficulty communicating, poor compliance, waste disposal issues, and increased viral load. There are insufficient data to quantify all of the adverse effects that might reduce the acceptability, adherence, and effectiveness of face masks.

[BMJ: mask related acne (“maskne”) and other facial dermatoses](https://www.bmj.com/content/373/bmj.n1304)

Travel-related control measures

Many countries have implemented measures including complete or partial closure of borders, entry or exit screening, and/or quarantine of travelers. Consult your local guidance.

Low- to very low-certainty evidence suggests that travel-related control measures may help to limit the spread of infection across national borders. Cross-border travel restrictions are likely to be more effective than entry and exit screening, and screening is likely to be more effective in combination with other measures (e.g., quarantine, observation).

Low-certainty evidence suggests that screening at travel hubs may slightly slow the importation of infected cases; however, the evidence base comes from two mathematical model studies and is limited by their assumptions. Evidence suggests that one-time screening in apparently healthy people may miss between 40% and 100% of people who are infected, although the certainty of this ranges from very low to moderate. In very low-prevalence settings, screening for symptoms or temperature may result in few false negatives and many true negatives, despite low overall accuracy. Repeated screenings may result in more cases being identified eventually and reduced harm from false reassurance.

A Cochrane review found quarantine to be important in reducing the number of people infected and deaths, especially when started earlier and when used in combination with other prevention and control measures. However, the current evidence is limited because most...
studies are based on mathematical modeling studies that make assumptions on important model parameters.[534]

- The psychosocial effects of enforced quarantine may have long-lasting repercussions.[535] [536]

Lifestyle modifications

- Lifestyle modifications (e.g., smoking cessation, weight loss) may help to reduce the risk of infection, and may be a useful adjunct to other interventions.[537]
- The WHO recommends that tobacco users stop using tobacco given the well-established harms associated with tobacco use and second-hand smoke exposure.[211] The UK Health Security Agency also recommends stopping smoking.


Patient discussions

General discussions

- Communicate with patients and their families and caregivers, and support their mental wellbeing to help alleviate any anxiety and fear they may have. Signpost to charities and support groups.[20]
- Explain that symptoms may include cough, fever, and loss of sense of smell or taste. Patients may also experience breathlessness (which may cause anxiety), delirium (which may cause agitation), fatigue, headache, myalgia, sore throat, drowsiness (particularly in older people), poor appetite, and chest discomfort/pain. Additional symptoms in children may include grunting, nasal flare, nasal congestion, poor appetite, gastrointestinal symptoms, skin rash, and conjunctivitis. The presence of fever, rash, abdominal pain, diarrhea, or vomiting in children may indicate pediatric inflammatory multisystem syndrome (PIMS). Reassure the patient that they are likely to feel much better in a week if their symptoms are mild.[20]
- Discuss who to contact if their symptoms get worse, or if PIMS is suspected. Offer telephone or video consultations as appropriate.[20]
- Discuss the benefits and risks of hospital admission or other acute care delivery services. Explain that people may deteriorate rapidly, and discuss future care preferences at the first assessment to give people who do not have existing advance care plans an opportunity to express their preferences.[20]

Pulse oximetry

- Patients may be required to use a pulse oximeter in the home setting. Patient education and appropriate follow-up are required.

- [Health Education England: adult pulse oximetry monitoring video] (https://www.youtube.com/watch?v=ifnYjD4IKus&t=141s)

Travel advice

- Travel restrictions vary across countries. Consult local guidance for specific recommendations in your country:

  - [NaTHNac: travel health pro] (https://travelhealthpro.org.uk)

Pets and animals

• Advise people with suspected or confirmed infection to avoid contact with animals, including pets, livestock, and wildlife. The risk of animals spreading severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to people is low. However, there is limited evidence that the virus can spread from people to certain animals (e.g., dogs, cats, mink, hamsters, ferrets, nonhuman primates, big cats and other zoo animals, some wildlife) during close contact.[1278]

Return to physical activity

• Recommend a phased return to exercise only when the patient has been symptom-free for at least 7 days. Advise patients to begin with at least 2 weeks of minimal exertion, and to use daily self-monitoring to track progress and decide whether to move up or drop back a phase. Patients who have a history of severe disease, cardiac involvement, ongoing symptoms, or adverse psychological symptoms require further clinical assessment before returning to physical activity.[1279]
• Guidance on return to sports in children is available from the American Academy of Pediatrics:
  • Clinical or subclinical myocarditis has been reported in competitive athletes with recent infection that restricts them from training and competitive play.[1280] Early recognition and continuous assessment of cardiac abnormality in competitive athletes is important to prevent cardiac complications.[1281]

General resources

Monitoring

Regularly monitor the following in hospitalized patients to facilitate early recognition of deterioration and monitor for complications:[87]

- Vital signs (temperature, respiratory rate, heart rate, blood pressure, oxygen saturation)
- Hematologic and biochemistry parameters
- Coagulation parameters (D-dimer, fibrinogen, platelet count, prothrombin time)
- ECG
- Chest imaging
- Signs and symptoms of venous or arterial thromboembolism.

Medical early warning scores

- Utilize medical early warning scores that facilitate early recognition and escalation of treatment of deteriorating patients (e.g., National Early Warning Score 2 [NEWS2], Pediatric Early Warning Signs [PEWS]) where possible.[87]
- There are a lack of data on the value of using these scores in patients with COVID-19 in the primary care setting.
  - A systematic review and meta-analysis found that the NEWS2 score had moderate sensitivity and specificity in predicting the deterioration of patients with COVID-19. The score showed good discrimination in predicting the combined outcome of the need for intensive respiratory support, admission to the intensive care unit, or in-hospital mortality.[571]
  - The sequential organ failure assessment (SOFA) score does not possess adequate discriminant accuracy for mortality prediction in patients prior to intubation for COVID-19 pneumonia.[1258]

Pregnant women

- Fetal well-being should be monitored. The frequency of fetal heart rate observations should be individualized based on gestational age, maternal clinical status (e.g., hypoxia), and fetal conditions.[87]

Post-discharge follow-up

- Patients who have had suspected or confirmed COVID-19 (of any disease severity) who have persistent, new, or changing symptoms should have access to follow-up care.[87]
- Guidelines for the respiratory follow-up of patients with COVID-19 pneumonia have been published. Follow-up algorithms depend on the severity of pneumonia, and may include clinical consultation and review (face-to-face or telephone) by a doctor or nurse, chest imaging, pulmonary function tests, echocardiogram, sputum sampling, walk test, and assessment of oxygen saturation.[1259]
- More than half of patients discharged from hospital had lung function and chest imaging abnormalities 12 weeks after symptom onset.[1260] Pulmonary function tests may reveal altered diffusion capacity, a restrictive pattern, or an obstructive pattern.[1261] Impaired diffusion capacity was more severe and recovered slower in females compared with males, and the first 3 months was the critical recovery period for diffusion capacity.[1262]

Prognostic scores

- Various prognostic and clinical risk scores are being researched or developed for COVID-19 (e.g., A-DROP, APACHE II, CALL, COPE, COVID-GRAM, COVID-19MRS, COVID-19 SEIMC, CVS, OurRisk-CoV, QCOVID, SCARP, SOARS, 3F, 4C).[1263][1264][1265][1266][1267][1268][1269][1270][1271][1272][1273][1274][1275][1276][1277] However, further external validation across various populations is needed before their use can be recommended.
• The World Health Organization recommends using clinical judgment, including consideration of the patient’s values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the intensive care unit, rather than currently available prediction models for prognosis.[87]
## Complications

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<tr>
<th>Complications</th>
<th>Timeframe</th>
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<tr>
<td>post-intensive care syndrome</td>
<td>variable</td>
<td>high</td>
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<td>Patients treated in the intensive care unit can present with post-intensive care syndrome, a spectrum of psychiatric, cognitive, and/or physical disability (e.g., muscle weakness, cognitive dysfunction, insomnia, depression, anxiety, post-traumatic stress disorder, delirium, encephalopathy) that affects survivors of critical illness, and persists after the patient has been discharged from the intensive care unit. Weakness affects 33% of patients who receive mechanical ventilation, 50% of patients with sepsis, and &lt;50% of patients who remain in the intensive care unit for more than 1 week. Cognitive dysfunction affects 30% to 80% of patients. The risk can be minimized with medication management, physical rehabilitation, family support, and follow-up clinics.[19] Physical, mental, or cognitive symptoms were reported frequently in patients who survived 1 year following intensive care unit.[1097]</td>
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<tr>
<td>thrombosis</td>
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<td>A hypercoagulable state is one of the hallmarks of disease, particularly in critically ill patients, often manifesting as venous and arterial thromboembolism. The coagulopathy in COVID-19 has a prothrombotic character, with increases in D-dimer, fibrin, fibrin degradation products, and fibrinogen.[1098] Antiphospholipid antibodies have been detected in patients with severe and critical disease; however, there does not currently appear to be any association between this finding and disease outcomes (e.g., thrombosis, mortality).[1099] Epidemiology: the pooled incidence of venous thromboembolism, deep vein thrombosis, and pulmonary embolism among hospitalized patients was 14.7%, 11.2%, and 7.8%, respectively. The prevalence was significantly higher in patients admitted to the intensive care unit, despite thromboprophylaxis. The prevalence of arterial thromboembolism appears to be lower at 3.9%; however, evidence is limited.[1100] Thromboembolic events are rare in children.[1101] The risk factors with the most evidence for being predictive of venous thromboembolism are older age and elevated D-dimer levels.[1102] Male sex, obesity, mechanical ventilation, intensive care unit admission, severe parenchymal abnormalities, and elevated white blood cells have also been identified as risk factors.[1103] Etiology: the pathogenesis is not completely understood. It has been hypothesized that local thrombi are formed due to a local inflammatory process, rather than the classical emboli coming from elsewhere in the body.[1104] [1105] Patients may be predisposed to thromboembolism due to the direct effects of infection, or the indirect effects of infection (e.g., severe inflammatory response, critical illness, traditional risk factors).[1106] Thrombotic events may be due to cytokine storm, hypoxic injury, endothelial dysfunction, hypercoagulability, and/or increased platelet activity.[1107] Diagnosis: monitor patients for signs or symptoms suggestive of venous or arterial thromboembolism, and proceed according to hospital protocols for diagnosis.[87] Management: treat patients with a thromboembolic event (or who are highly suspected to have thromboembolic disease if imaging is not possible) with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19. Low molecular weight heparin or unfractionated heparin is preferred over oral anticoagulants. Treat patients who require extracorporeal membrane oxygenation or continuous renal replacement therapy, or who have thrombosis of catheters or extracorporeal filters, with antithrombotic therapy as per the standard institutional protocols for those without COVID-19.[19] Monitoring: hematologic and coagulation parameters are commonly measured in hospitalized patients; however, there is currently insufficient evidence to recommend either for or against using such data to guide management decisions. Patients with very high D-dimer levels have the greatest risk of thrombosis and may benefit from active monitoring.[740] [741]</td>
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Complications | Timeframe | Likelihood
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Prognosis: patients with thromboembolic events have 1.93 times the odds of dying compared with patients without venous thromboembolism.[1108]

Also see Disseminated intravascular coagulation below.

| cardiovascular complications | variable | high |
Cardiovascular complications include arrhythmias, myocardial injury, acute coronary syndrome, and heart failure.[1109]

Epidemiology: cardiovascular complications have been reported in 14.1% of patients during hospitalization.[1109] The overall pooled incidence of acute myocardial infarction, heart failure, arrhythmias, cardiac arrest, and acute coronary syndrome were 21%, 14%, 16%, 3.45%, and 1.3%, respectively.[1110] Higher rates of myocardial injury have been reported in the US (9% to 52%) compared with China (7% to 28%).[1111] A Cochrane review found that the most common cardiovascular complications were arrhythmias, heart failure, and arterial and venous occlusive events.[168] More rarely, cases of fulminant myocarditis, pericarditis, cardiac tamponade, cor pulmonale, and takotsubo syndrome have been reported.[1112] [1113] [1114] [1115] [1116] [1117] Risk factors include older age, hypertension, underlying cardiovascular disease, and chronic kidney disease.[1111]

Etiology: COVID-19 is associated with a high inflammatory burden. Inflammation of the myocardium can result in myocarditis, heart failure, arrhythmias, acute coronary syndrome, rapid deterioration, and sudden death.[1118] [1119]

Diagnosis: perform an ECG and order high-sensitivity troponin I (hs-cTnI) or T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients with symptoms or signs that suggest acute myocardial injury in order to make a diagnosis. The following test results may help inform the diagnosis: evolving ECG changes suggesting myocardial ischemia; NT-proBNP level >400 nanograms/L; high levels of hs-cTnI or hs-cTnT, particularly levels increasing over time. Elevated troponin levels may reflect cardiac inflammatory response to severe disease rather than acute coronary syndrome. Seek specialist cardiology advice on further tests and imaging.[20]

Management: seek specialist cardiology advice on treatment and follow local treatment protocols.[20] There are limited data to recommend any specific drug treatments for these patients. Involve a multidisciplinary team including intensive care specialists, cardiologists, and infectious disease specialists.[1120]

Monitoring: monitor blood pressure, heart rate, and fluid balance, and perform continuous ECG monitoring in all patients with suspected or confirmed acute myocardial injury. Monitor in a setting where cardiac or respiratory deterioration can be rapidly identified.[20] Laboratory biomarkers may help identify those at greater risk of developing cardiovascular complications. Elevated cardiac biomarkers and emerging arrhythmias are associated with the development of severe disease and need for intensive care admission.[1121]

Prognosis: myocardial injury is associated with poor outcomes and survival. Elevated troponin predicts a poor outcome and higher risk of mortality.[1111] An overall case fatality rate of 9.6% has been reported.[1109] Infection may have longer-term implications for overall cardiovascular health.[1122] Cardiovascular problems have been reported up to 1 year after infection, including in those who were not hospitalized for the acute infection.[1123]

| acute kidney injury | variable | high |
Acute kidney injury is common, particularly in critically ill patients. It can develop at any time before, during, or after hospital admission.[20]

Epidemiology: the pooled incidence of acute kidney injury has been estimated to be 19.45%; however, incidence varies across studies. Patients have a significantly increased risk of in-hospital mortality.
Complications | Timeframe | Likelihood
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(54.2%).[1124] Independent risk factors included male sex, older age, smoking history, obesity, hypertension, diabetes, pneumopathy, cardiovascular disease, cancer, chronic kidney disease, mechanical ventilation, and use of vasopressors.[1125]

Etiology: causes include hemodynamic changes, hypovolemia, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathalogy, or rhabdomyolysis. May be associated with hematuria, proteinuria, and abnormal serum electrolyte levels (e.g., potassium, sodium).[20]

Diagnosis: monitor patients for signs or symptoms suggestive of acute kidney injury, and proceed according to hospital protocols for diagnosis.

Management: follow local guidelines for managing acute kidney injury. Supportive measures and fluid management are required.[1124] Potassium binders may be used as options alongside standard care for the emergency management of acute life-threatening hyperkalemia.[20] Continuous renal replacement therapy (CRRT) is recommended in critically ill patients with acute kidney injury who develop indications for renal replacement therapy; prolonged intermittent renal replacement therapy is recommended over hemodialysis if CRRT is not available or possible.[19]

Monitoring: monitor patients with chronic kidney disease for at least 2 years after acute kidney injury.[20]

**post-COVID-19 syndrome (long COVID)**

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Also known as post-acute COVID-19, post-acute COVID-19 syndrome, chronic COVID, long-haul COVID, post-acute sequelae of SARS-CoV-2 infection (PASC), and post-COVID conditions.

Definition: case definitions vary. The World Health Organization defines it as a condition that occurs in people with a history of probable or confirmed SARS-CoV-2 infection, usually occurring 3 months from the onset of symptoms and lasting for at least 2 months, that cannot be explained by an alternative diagnosis.[1126] The UK National Institute for Health and Care Excellence defines post-COVID-19 syndrome as signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis. Ongoing symptomatic COVID-19 is defined as signs and symptoms from 4 weeks up to 12 weeks. The term long COVID may be used to describe either of these case definitions.[1008] The Centers for Disease Control and Prevention defines post-COVID conditions as an umbrella term for the wide range of health consequences that are present more than 4 weeks after infection with SARS-CoV-2.[1127] The syndrome is not thought to be linked to disease severity during the acute phase of illness.[1008] Protracted symptoms are common after many viral and bacterial infections, including influenza. However, while the clinical features were also observed after influenza infection, the incidence appears to be higher after COVID-19.[1128] The neurologic symptoms are similar to symptoms of other neurologic conditions such as chronic fatigue syndrome and functional neurologic disorder.[1129] Evidence from a cross-sectional analysis of a large, population-based cohort suggests that persistent physical symptoms after COVID-19 may be associated more with the belief in having been infected than with having laboratory-confirmed infection. Laboratory-confirmed infection was associated only with anosmia. Findings suggest that persistent physical symptoms after infection should not be automatically ascribed to COVID-19, but further research is required.[1130]

Epidemiology: frequency ranges from 4.7% to 80% across observational studies, and occurs between 3 to 24 weeks after the acute phase or hospital discharge. Potential risk factors include older age, age 40 to 49 years, female sex, obesity, severe clinical status, higher number of comorbidities, higher symptom load, hospital admission, and oxygen supplementation in the acute phase, although data is lacking.[1131][1132][1133] Approximately 63% of patients report at least one symptom at 30 days after symptom onset/hospitalization, with 71% reporting at least one symptom after 60 days, and 46% at 90 days or more in a systematic review and meta-analysis.[1134] In another systematic review, 54% of patients reported at least one symptom at 1 month, 55% of patients reported at least one symptom at 2 to 5 months, and 54% of patients reported at least one symptom at 6 months or longer.[1135] However, some studies report much lower rates of continuing symptoms after 12 weeks (2.3% to 3%).[1136][1137] Persistent symptoms have been reported up to 12 months after discharge, but most people had a good and functional recovery during 1-year follow-up.[1138][1139] Prolonged illness can occur among young
Complications | Timeframe | Likelihood
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adults with no underlying comorbidities, and in patients who had mild disease. Approximately 12% to 15% of patients who had mild symptoms still had symptoms up to 8 months later. The number of symptoms at follow-up was associated with the symptom load during the acute phase of infection and the number of comorbidities in nonhospitalized patients. Persistent symptoms have been reported in pregnant women and children, but appear to be less common in children compared with adults. The frequency and characteristics of this syndrome are still under investigation in children and adolescents.

Diagnosis: use a holistic, person-centered approach that includes a comprehensive clinical history (including history of suspected or confirmed acute COVID-19, nature and severity of previous and current symptoms, timing and duration of symptoms since the start of acute illness, and a history of other health conditions), and appropriate examination that involves assessing physical, cognitive, psychological, and psychiatric symptoms, as well as functional abilities. Refer patients with signs or symptoms that could be caused by an acute or life-threatening complication (e.g., severe hypoxemia, signs of severe lung disease, cardiac chest pain, multisystem inflammatory syndrome in children) urgently to the relevant acute services. After ruling out acute or life-threatening complications and alternative diagnoses, consider referring people to an appropriate service, such as an integrated multidisciplinary assessment service, any time from 4 weeks after the start of acute COVID-19.

Signs and symptoms: symptoms vary widely, may relapse and remit or fluctuate, can change unpredictably, and can occur in those with mild disease only. Common long-term symptoms include, but are not limited to, persistent cough, low-grade fever, breathlessness, weakness, malaise, impairment of concentration, fatigue, pain, chest pain/tightness, palpitations, myalgia, arthralgia, headaches, vision changes, hearing loss, earache, tinnitus, sore throat, loss of taste/smell, nasal congestion, impaired mobility, peripheral neuropathy, dizziness, tremors, memory loss, mood changes, skin rashes, hair loss, gastrointestinal symptoms, neurocognitive difficulties, sleep disturbances, delirium (older people), and mental health conditions (e.g., anxiety, depression, post-traumatic stress disorder). Children and older people may not have the most commonly reported symptoms. The following symptoms and signs are less commonly reported in children and younger people: dyspnea; persistent cough; pain on breathing; palpitations; heart rate variations; chest pain. The most common symptoms at 1-year follow-up were fatigue, sweating, chest tightness, anxiety, and myalgia. Some of the symptoms may overlap with post-intensive care syndrome (see above). An increased risk of incident diabetes has been reported in the post-acute phase up to 12 months. The inability to return to normal activities, emotional and mental health outcomes, and financial loss are common.

Investigations: tailor investigations to the clinical presentation, and to rule out any acute or life-threatening complications and alternative diagnoses. Investigations may include blood tests (e.g., complete blood count, kidney and liver function tests, C-reactive protein, ferritin, B-type natriuretic peptide, glycosylated hemoglobin [HbA1c], thyroid function), oxygen saturation, blood pressure and heart rate measurements, exercise tolerance test, chest imaging, electrocardiogram, and psychiatric assessment. Approximately 50% of patients had residual abnormalities on chest CT and pulmonary function tests at 3 months. Around 9% of patients had deteriorating chest x-ray appearances at follow-up, which may indicate lung fibrosis. Persistently elevated D-dimer and C-reactive protein have also been reported. The prevalence of pulmonary fibrosis has been reported as 44.9% in one meta-analysis.

Management: give advice and information on self-management including ways to self-manage symptoms (e.g., set realistic goals, antipyretic for fever, breathing techniques for chronic cough, home pulse oximetry for monitoring breathlessness, pulmonary rehabilitation, staged return to exercise); who to contact if there is concern about symptoms or if there is need for support; sources of support (e.g., support groups, online forums); and how to get support from other services (e.g., social care, housing, financial support). There is a lack of evidence for pharmacologic interventions to treat the condition. A personalized, multidisciplinary rehabilitation plan that covers physical, psychological, and psychiatric aspects of rehabilitation is an important part of management. Many patients recover spontaneously with holistic support, rest, symptomatic treatment, and a gradual increase in activity. Referral to a specialist may be required in patients where there is clinical concern along with respiratory, cardiac, or neurologic symptoms that are new, persistent, or progressive. Consensus guidelines on the specific management of fatigue, breathing discomfort, and cognitive symptoms are also available from the American Academy of Physical Medicine and Rehabilitation.
Follow-up: recovery time differs but symptoms resolve by 12 weeks in most people. Agree with the patient how often follow-up and monitoring are needed (either in person or remotely), and which healthcare professionals should be involved. Take into account the patient's level of need and the services involved. Tailor monitoring to the patient's symptoms, and consider supported self-monitoring at home (e.g., heart rate, blood pressure, pulse oximetry). Be alert to symptoms that could require referral or investigation.[1008]

[BMJ: management of post-acute covid-19 in primary care] (https://www.bmj.com/content/370/bmj.m3026)
[BMJ: long covid - mechanisms, risk factors, and management] (https://www.bmj.com/content/374/bmj.n1648)

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<tr>
<td>acute liver injury</td>
<td>variable</td>
<td>medium</td>
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Liver injury may be associated with preexisting liver disease, viral infection, drug toxicity, systemic inflammation, hypoxia, or hemodynamic issues; however, the underlying mechanism is unclear. The overall prevalence has been reported as 25%, although there is no uniform definition of liver injury in these patients and prevalence depends on the definition used in studies. The overall prevalence may be as low as 9% when strict criteria for diagnosis are used. The prevalence of elevated alanine aminotransferase and aspartate aminotransferase was 19% and 22%, respectively. The prevalence of hypertransaminasemia was higher in patients with severe disease compared with patients with nonsevere disease.[1154] Another meta-analysis concluded that findings from the available evidence to date from observational studies and case reports indicate that transaminases and total bilirubin levels appear not to significantly change in patients with COVID-19.[1155]

Risk factors associated with severe liver injury include older age, preexisting liver disease, and severe disease.[1156] Medications used in the treatment of COVID-19 (e.g., remdesivir, tocilizumab) may have a detrimental effect on liver injury.[1157] Guidelines on the management of liver derangement in patients with COVID-19 have been published.[1158]

| neurologic complications   | variable  | medium     |

Neurologic complications include acute cerebrovascular disease, impairment of consciousness, ataxia, seizures, status epilepticus, encephalopathy, encephalitis and meningoencephalitis, acute disseminated encephalomyelitis, corticospinal tract signs, demyelinating lesions, peripheral neuropathies, cerebral venous sinus thrombosis, myopathy, Guillain-Barre syndrome, dementia, and abnormal findings on brain magnetic resonance imaging.[1159]

Patients commonly have central or peripheral neurologic complications, possibly due to viral invasion of the central nervous system, inflammatory response, or immune dysregulation.[1160] Neurologic complications occur across the lifespan in the context of infection, with and without known comorbidities, and with all disease severities (including asymptomatic patients).[1161] Patients may present with these manifestations, or they may develop them during the course of the disease (usually 1 to 2 weeks after the onset of respiratory disease).[1162] Patients with preexisting neurologic disorders may develop an exacerbation of their neurologic symptoms.[1163] Long-term sequelae may be possible.[1164]

Epidemiology: reported in 22% to 35% of patients. Central nervous system manifestations were more common than peripheral nervous system manifestations.[1159] Neurologic involvement is common in children and adolescents (22% in patients ages <21 years).[1165]

Acute cerebrovascular disease: (including ischemic stroke, hemorrhagic stroke, cerebral venous thrombosis, and transient ischemic attack) has been reported in 0.5% to 5.9% of patients. The most common type was ischemic stroke (0.4% to 4.9%).[1160] Patients with severe disease are at an increased risk of ischemic stroke compared with patients with nonsevere disease.[1166] Stroke is relatively frequent among hospitalized patients relative to other viral respiratory infections, and has a high risk of in-hospital mortality. Risk factors include older age and male sex. Median time from onset of COVID-19 symptoms to stroke was 8 days.[1167][1168] Stroke presents later in severe disease, and earlier in mild to moderate...
Coronavirus disease 2019 (COVID-19)

Follow up

Complications | Timeframe | Likelihood
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disease.[1169] Patients may present with ischemic stroke during the convalescent phase of infection, including younger people <50 years of age with asymptomatic or pauci-symptomatic COVID-19.[1170] Ischemic stroke appears to be more severe and result in worse outcomes (severe disability) in patients with COVID-19, with the median NIH Stroke Scale score being higher among those with COVID-19 compared with those without.[1171] Guidelines for the management of acute ischemic stroke in patients with COVID-19 infection have been published.[1172]

Guillain-Barre syndrome: both post-infectious and pre-infectious patterns have been reported.[1160] The pooled prevalence among hospitalized and nonhospitalized patients was 0.15%.[1173] The mean age of patients was 55 years with a male predominance. Most patients had respiratory and/or severe symptoms of COVID-19, although it has also been reported in asymptomatic patients. A higher prevalence of the classic sensorimotor form and acute inflammatory demyelinating polyneuropathy have been reported, although rare variants have also been noted.[1174] Patients had an increased odds for demyelinating subtypes. Clinical outcomes were comparable to those for contemporary or historical controls not infected with SARS-CoV-2.[1173]

Encephalitis: has been reported in <1% of patients overall, but increases up to 6.7% in critically ill patients. Encephalitis is associated with poorer outcomes including admission to the intensive care unit, need for mechanical ventilation, and increased mortality rate (13.4%) compared with the general population of COVID-19 patients.[1175] Rare cases of autoimmune encephalitis have been reported.[1176]

cardiac arrest | variable | medium
--- | --- | ---
In-hospital cardiac arrest is common in critically ill patients, and is associated with poor survival, particularly among older patients. Among 5019 critically ill patients with COVID-19, 14% had an in-hospital cardiac arrest. Risk factors included older age, male sex, presence of comorbidities, and admission to a hospital with a smaller number of intensive care unit beds. Approximately 57% of patients received cardiopulmonary resuscitation. The most common rhythms at the time of resuscitation were pulseless electrical activity (49.8%) and asystole (23.8%). Of those who received resuscitation, 12% survived to hospital discharge with most of these patients being younger than 45 years of age.[1177]

pregnancy-related complications | variable | medium
--- | --- | ---
Pregnancy outcome is usually good, although there are little data on exposure during early pregnancy.[37] The risk for complications was higher in pregnant women who were symptomatic.[1178]

Maternal outcomes: the odds of admission to the intensive care unit, invasive ventilation, and need for extracorporeal membrane oxygenation were higher in pregnant and recently pregnant women compared with nonpregnant reproductive-aged women. Pregnant women may also be at an increased risk of maternal death. Risk factors for serious complications include preexisting comorbidities (e.g., chronic hypertension, diabetes), high maternal age, non-White ethnicity, presence of pregnancy-specific conditions (e.g., gestational diabetes, preeclampsia), and high body mass index.[35] [36] A statistically significant higher risk of gestational diabetes, gestational hypertension, poor fetal growth, and preeclampsia was reported in pregnant women during the pandemic period compared with the prepandemic period.[1179]

Preterm birth: preterm birth was more common in pregnant women with COVID-19 compared with pregnant women without the disease. However, the overall rates of spontaneous preterm births in pregnant women with COVID-19 was broadly similar to those observed in the prepandemic period, so these preterm births could have been medically indicated.[35] [36]

Stillbirth and neonatal death: the overall rates of stillbirths and neonatal deaths do not seem to be higher than the background rates.[35] [36] [1180] In England, there is no evidence of an increase in stillbirths regionally or nationally during the pandemic when compared with the same months in the previous year and despite variable community infection rates in different regions.[1181] However, in the US, women with COVID-19 were at an increased risk for stillbirth compared with women without COVID-19 during the period of March 2020 to September 2021, with the magnitude of association being higher during the Delta variant predominance.[1182]
### Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>Neonatal infection: limited low-quality evidence suggests that the risk of infection in neonates is extremely low. Most infections are acquired in the postpartum period, although congenitally acquired infection has been reported. Unlike children who generally have asymptomatic infection, two-thirds of neonatal cases are symptomatic and a significant proportion require intensive care, although the overall prognosis appears to be excellent.[35] [36] [1183] [1184]</td>
<td>variable</td>
<td>low</td>
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<tr>
<td>sepsis/septic shock</td>
<td>variable</td>
<td>low</td>
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<tr>
<td>Sepsis (diagnosed according to Sepsis-3 or according to the presence of infection-related organ dysfunction necessitating organ support/replacement) has been reported in 78% of intensive care unit patients and 33% of hospitalized patients.[1185] Guidelines for the management of shock in critically ill patients with COVID-19 recommend a conservative fluid strategy (crystalloids preferred over colloids, buffered/balanced crystalloids preferred over unbalanced crystalloids) and a vasoactive agent. Norepinephrine (noradrenaline) is the preferred first-line agent. Vasopressin or epinephrine (adrenaline) can be added to norepinephrine if target mean arterial pressure cannot be achieved with norepinephrine alone.[19] [816] Ultimately, patients who require fluid resuscitation or hemodynamic management of shock should be treated and managed identically to patients with septic shock.[19]</td>
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<td>low</td>
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<tr>
<td>disseminated intravascular coagulation</td>
<td>variable</td>
<td>low</td>
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<tr>
<td>Disseminated intravascular coagulation (DIC) is a manifestation of coagulation failure, and an intermediate link in the development of multi-organ failure. Patients may be at high risk of bleeding/hemorrhage or venous thromboembolism.[1186] The pooled incidence of DIC is 3%, and it is associated with poor prognosis. The incidence was higher in patients with severe disease and those admitted to the intensive care unit, and in nonsurvivors compared with survivors.[1187] COVID-19-associated coagulopathy appears to be distinct from DIC, although DIC has been reported in severely affected patients. The coagulation changes in COVID-19 patients mimic, but are not identical to, DIC, and the vast majority of patients do not meet the criteria for usual forms of DIC.[1188] Coagulopathy manifests as elevated fibrinogen, elevated D-dimer, and minimal change in prothrombin time, partial thromboplastin time, and platelet count in the early stages of infection. Increasing interleukin-6 levels correlate with increasing fibrinogen levels. Coagulopathy appears to be related to severity of illness and the resultant thromboinflammation. Monitor D-dimer level closely.[1189] Anticoagulant therapy with a low molecular weight heparin or unfractionated heparin has been associated with a better prognosis in patients with severe COVID-19 who have a sepsis-induced coagulopathy (SIC) score of ≥4 or a markedly elevated D-dimer level.[1190] In patients with heparin-induced thrombocytopenia (or a history of it), argatroban or bivalirudin are recommended.[1186] Standard guidance for the management of bleeding manifestations associated with DIC or septic coagulopathy should be followed if bleeding occurs; however, bleeding manifestations without other associated factors is rare.[891] [1189]</td>
<td>variable</td>
<td>low</td>
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<tr>
<td>acute respiratory failure</td>
<td>variable</td>
<td>low</td>
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<tr>
<td>The leading cause of death is respiratory failure from acute respiratory distress syndrome.[1017] Children can quickly progress to respiratory failure.[1191] Patients with COVID-19 may have a higher risk of developing ventilator-associated pneumonia compared with patients without COVID-19. Overall, ventilator-associated pneumonia was reported in 48.2% of mechanically ventilated patients and the mortality rate was 51.4%.[1192]</td>
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<td>low</td>
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<tr>
<td>air leak</td>
<td>variable</td>
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<tr>
<td>Air leak (pneumothorax, pneumomediastinum, and subcutaneous emphysema) is associated with higher mortality and longer hospital stay, especially in older people, and can occur even without positive pressure</td>
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</table>
Complications | Timeframe | Likelihood
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ventilation. It is mainly due to disease progression resulting in inflammatory insult to lung parenchyma and ventilatory stress-induced alveolar damage. The incidence varies widely across studies and increases with disease severity. The mean age of patients was 58 years and 75% were male. Hypertension was the most common comorbidity, followed by diabetes. Isolated pneumothorax was the most common type of air leak (48.5%), with 17% of patients developing a spontaneous pneumothorax. Mortality was 40%. Further research is required.[1193]

cytokine release syndrome | variable | low
Some patients with severe disease have laboratory evidence of an unregulated inflammatory response similar to cytokine release syndrome, characterized by plasma leakage, increased vascular permeability, diffuse intravascular coagulation, and immunodeficiency. These patients have a poor prognosis. High serum levels of proinflammatory cytokines, particularly interleukin-6, have been identified in these patients. Features of secondary hemophagocytic lymphohistiocytosis may be present. Treatment options include interleukin-6 inhibitors (e.g., tocilizumab), Janus kinase inhibitors (e.g., baricitinib), and anakinra.[1194]

Also see Pediatric inflammatory multisystem syndrome, a cytokine release syndrome-like illness in children, below.

pediatric inflammatory multisystem syndrome (PIMS) | variable | low
Also known as multisystem inflammatory syndrome in children (MIS-C), pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), as well as other variations. Multisystem inflammatory syndrome in adults (MIS-A) has also been reported, albeit more rarely.[1195][1196]

Definition: a rare but serious delayed complication that may develop in children and adolescents approximately 3 to 4 weeks (or longer) after the onset of acute infection, likely due to a postinfectious inflammatory process. The syndrome resembles, but is distinct from, Kawasaki disease, and also shares common features with toxic shock syndrome. It has a strong temporal association with SARS-CoV-2 infection,[1197] The case definition generally includes the presence of fever, elevated inflammatory markers, multi-organ dysfunction, a history of a positive SARS-CoV-2 test (or close contact with a confirmed case), and no plausible alternative diagnosis. However, case definitions vary.[541] [1198] [1199] Can occur rarely after COVID-19 vaccination.[1200] [1201]

Epidemiology: the risk of MIS-C within 2 months of confirmed infection was 0.05% in one Danish cohort study.[1202] A systematic review found that the median age of patients was 9.3 years of age, and 57% of patients were male. At least one comorbidity was reported in 31% of cases, most commonly obesity, asthma, and chronic lung disease.[1203] Factors associated with more severe outcomes included age >5 years; non-Hispanic Black ethnicity; symptoms of dyspnea or abdominal pain; elevated C-reactive protein, troponin, ferritin, D-dimer, brain natriuretic peptide, or interleukin-6; and reduced lymphocyte or platelet counts.[1204] Cases have been reported rarely in neonates (temporally associated with prenatal exposure), and there may be a higher risk of mortality in neonates compared with older children.[1205]

Diagnosis: patients often have predominant cardiac dysfunction and gastrointestinal symptoms. The most common manifestations were fever (99%), gastrointestinal symptoms (87%), shock (66%), rash (59%), conjunctivitis (57%), cardiovascular manifestations (55%), oral mucosal changes (42%), respiratory symptoms (41%), neurologic symptoms (36%), and coronary artery aneurysms (22%).[1203] The pooled prevalence of significant left ventricular dysfunction was 38%, coronary aneurysm or dilatation was 20%, and ECG abnormalities/cardiac arrhythmias was 28%.[1206] Neonates commonly present with cardiorespiratory compromise.[1205] Three types of clinical manifestations have been recognized: persistent fever and gastrointestinal symptoms (the most common type); shock with heart dysfunction; and symptoms coincident with the diagnostic criteria for Kawasaki disease.[1207]

Investigations: inflammatory and cardiac markers were elevated in the majority of patients, and 38% had abnormal findings on chest x-ray.[1203] Raised serum troponin level was reported in 33% of patients, and raised pro B-type natriuretic peptide (proBNP)/BNP level was reported in 44% of patients.[1206]
Complications | Timeframe | Likelihood
--- | --- | ---
Management: management is mainly supportive and involves a multidisciplinary team. Approximately 79% of patients required intensive care admission, 63% required inotropic support, 57% required anticoagulation, and 33% required mechanical ventilation.[1203] The optimal choice and combination of immunomodulating therapies have not been definitively established. The World Health Organization recommends corticosteroids in addition to supportive care (rather than either intravenous immune globulin plus supportive care, or supportive care alone) in hospitalized children ages 0 to 18 years who meet the standard case definition. It also recommends corticosteroids in addition to supportive care in those who meet both a standard case definition for MIS-C and diagnostic criteria for Kawasaki disease.[87] In the US, the National Institutes of Health guidelines panel recommends initial therapy with a combination of immunomodulatory therapy (i.e., intravenous immune globulin plus a low-to-moderate dose of corticosteroid) and antithrombotic therapy (i.e., low-dose aspirin plus anticoagulation in certain patients). Children who do not improve within 24 hours should be started on either anakinra, high-dose corticosteroids, or infliximab.[19] Guidance has also been published by the American College of Rheumatology.[1208] Consult your local guidelines for further information.

Prognosis: the majority of patients had good outcomes with no significant medium- or long-term sequelae at 1-year follow-up.[1209] Follow-up at 6 months found that while cardiac, gastrointestinal, renal, hematologic, and otolaryngology outcomes largely resolved at 6 months, muscular fatigue and emotional lability were common.[1210] The mortality rate was 1.9%.[1203]

Future COVID-19 vaccination: there are limited data on the safety of COVID-19 vaccines in people who have had MIS-C or MIS-A and who have not yet received a vaccine. A history of MIS-C or MIS-A is a precaution for vaccination.[364] Consult your local guidelines for more information.

vaccine-induced immune thrombocytopenia and thrombosis (VITT) | variable | low

Also known as thrombosis with thrombocytopenia syndrome (TTS) and vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). Evidence on this syndrome is limited.

Definition: prothrombotic disorder of thrombosis with concurrent thrombocytopenia and development of antiplatelet factor 4 (anti-PF4) antibodies occurring after vaccination with an adenovirus vector-based COVID-19 vaccine (e.g., AstraZeneca, Janssen). Thrombosis occurs in uncommon sites (e.g., cerebral venous sinus thrombosis, splanchnic vein thrombosis, arterial thrombosis) and may be multifocal. The syndrome clinically resembles heparin-induced thrombocytopenia. The exact pathophysiology remains unknown, but there are several hypotheses. Can be rapidly progressive and fatal.[1211] [1212] Cases have also been reported with mRNA vaccines, albeit more rarely.[419]

Epidemiology: observational data from the UK suggest the risk for a thrombotic event was highest in people ages <40 years, at 16.1 and 36.3 per million doses, respectively, for cerebral venous thrombosis or another thrombosis event, with the greatest elevated risk within 4 to 13 days after vaccination.[1213] Cases have been reported up to 48 days after vaccination.[1214]

Diagnosis: advise vaccine recipients who experience any severe symptoms from around 4 to 30 days after vaccination to seek urgent medical attention.[1215] [1216] Approximately half of patients present with cerebral venous sinus thrombosis.[1217] Headache is the most common presenting symptom, and may precede VITT by several days.[1218] [1219] Signs and symptoms include: new-onset headache that is getting worse and does not respond to simple analgesics; an unusual headache that seems worse when lying down or bending over, or may be accompanied by blurred vision, nausea and vomiting, speech difficulty, weakness, drowsiness, or seizures; new unexplained pinprick bruising or bleeding; and shortness of breath, chest pain, leg swelling, or persistent abdominal pain. Ask about vaccination history in people with suspected VITT. Refer people who are acutely unwell to the emergency department immediately.[1216] Patients may rarely present with ischemic stroke.[1220] Report all cases to local health authorities and through local vaccine adverse event reporting systems.

Investigations: order a complete blood count (with platelets), coagulation screen (including fibrinogen and D-dimer), blood film/peripheral smear, and platelet factor 4 enzyme-linked immunosorbent assay for
any patient presenting with acute thrombosis or new-onset thrombocytopenia within 30 days of receiving a COVID-19 vaccination. Typical laboratory features include thrombocytopenia, raised D-dimer levels above the level expected for venous thromboembolism, and low or normal fibrinogen. Antibodies to platelet factor 4 have also been identified. Order same-day imaging studies based on location of symptoms to confirm the site of thrombosis. Repeat imaging may be required in patients whose blood tests suggest probable VITT, but no thrombosis is seen on initial imaging or there is clinical or laboratory suspicion of progression.[1216] [1221] [1222] [1223] [1224]

Differential: other possible causes of thrombocytopenia with thrombosis include cancer, antiphospholipid syndrome, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, and paroxysmal nocturnal hemoglobinuria. Consider alternative diagnoses in people whose blood tests indicate it is unlikely they have VITT. A small number of people with VITT do not have thrombocytopenia at presentation. Therefore, repeat a complete blood count after 2 to 3 days or if symptoms worsen, if a high clinical suspicion of VITT remains. Discuss the need for further investigations with a hematologist.[1216]

Management: promptly treat patients. Consult a hematologist when making decisions about starting or adding treatments. There is limited information about the optimal treatment of this condition; however, management is similar to heparin-induced thrombocytopenia. First-line treatment is urgent administration of intravenous immune globulin. A second dose may be considered if there is an inadequate response after 2 to 3 days. Some experts also recommend the use of corticosteroids, especially if intravenous immune globulin treatment is insufficient. Anticoagulate with a nonheparin-based therapy such as a direct oral anticoagulant, fondaparinux, danaparoid, or argatroban, depending on the clinical picture, as soon as the benefit outweighs the risk of bleeding. Review response to anticoagulation if the patient’s clinical condition changes, and adjust treatment if needed. Avoid platelet transfusions, heparin (including heparin flushing solution), low molecular weight heparin, and vitamin K antagonists (e.g., warfarin). Consider plasma exchange, fibrinogen replacement, or rituximab in select patients. Some patients may require surgery to treat thrombosis.[1216] [1221] [1222] [1223] [1224]

Monitoring: after discharge, the patient should be under the care of a hematologist. Assess symptoms and measure D-dimer, fibrinogen, and platelet counts every 2 to 3 days for the first 2 weeks. Repeat enzyme-linked immunosorbent assay (ELISA) for platelet factor 4 antibodies weekly for the first 4 weeks. Repeat tests monthly for the first 6 months and, if no relapses occur, reduce the frequency of testing to every 3 months. When platelet 4 antibodies are no longer detected, review the need for ongoing treatment and monitoring.[1216]

Prognosis: mortality due to complications has been reported to be 39%.[1218] Fibrinogen levels, age, platelet count, and the presence of intracerebral hemorrhage or cerebral venous thrombosis are significantly associated with an increased risk of mortality.[1225]

Management is evolving and there are differences between the guidelines available. Consult the most current local guidelines for more detailed information on the diagnosis and management of this condition. Consult local guidelines for advice on further vaccination after an episode of VITT.


<table>
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<tr>
<th>aspergillosis</th>
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COVID-19-associated aspergillosis (CAPA) may occur in people who are critically ill. It is a recognized cause of a patient’s clinical condition not improving despite treatment.[20]
## Complications

<table>
<thead>
<tr>
<th>Epidemiology: reported in 10.2% of patients admitted to the intensive care unit in one study.[1226] Risk factors include older age, chronic lung disease, intubation for more than 7 days, immunosuppression, and use of high-dose corticosteroids.[20] [1227]</th>
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### Timeframe & Likelihood

**Epidemiology:** reported in 10.2% of patients admitted to the intensive care unit in one study.[1226] Risk factors include older age, chronic lung disease, intubation for more than 7 days, immunosuppression, and use of high-dose corticosteroids.[20] [1227]

**Diagnosis:** consider diagnosis in patients who deteriorate despite optimal supportive care or who have other suspicious radiologic or clinical features.[20] [1227] There are no specific signs or symptoms. Base your decisions on individual risk factors and the person's clinical condition, and involve a multidisciplinary team (including an infectious disease specialist).[20] Refer to your local protocols on the diagnosis of CAPA.

**Investigations:** use a range of tests to increase the likelihood of a confident diagnosis; include bronchoalveolar lavage, if possible. Test for antifungal resistance if an Aspergillus isolate is cultured. Do not order tests if there is a low clinical suspicion.[20]

**Management:** antifungal therapy is recommended. Only use antifungal therapy if investigations support a diagnosis of CAPA, or CAPA is suspected but the results of investigations are not available yet. There is not enough evidence to recommend specific antifungals. Discuss treatment options with a multidisciplinary team (including an infectious disease specialist). Stop treatment if the results of investigations do not support the diagnosis.[20] Refer to your local protocols on the management of CAPA.

**Prognosis:** a mortality rate of 54.9% was reported in one study.[1226]

### mucormycosis

- **Epidemiology:** as of June 2021, 275 cases were reported globally, with 85% of cases reported in India. Cases in India increased significantly during its second wave in early 2021.[1230] Cases have been reported in other countries, including the US.[1231] Risk factors include male sex, uncontrolled diabetes, and immunosuppression (e.g., due to corticosteroid therapy).[1232] [1233]

- **Diagnosis:** have a low threshold of suspicion for diagnosis. It is important not to miss warning signs and symptoms (e.g., nasal congestion; blackish/bloody nasal discharge; sinus or facial pain; toothache or loosening of teeth; vision disturbances; hemoptysis; necrotic eschar on skin, palate, or nasal turbinates). Do not hesitate to order appropriate investigations.[1234] The median time to interval between diagnosis of COVID-19 and evidence of mucormycosis was 15 days. Rhino-orbital mucormycosis was most common (42%), followed by rhino-orbito-cerebral mucormycosis (24%), and pulmonary mucormycosis (10%).[1232] Cases of atypical-site mucormycosis have been reported, as well as cases in COVID-19 recovered patients.[1235] [1236] Do not hesitate to aggressively order investigations as appropriate for detecting fungal etiology.[1234] Flexible bronchoscopy and chest imaging are recommended to enable early diagnosis of pulmonary mucormycosis.[1237]

- **Management:** management strategies include: controlling hyperglycemia, diabetes, or diabetic ketoacidosis; reducing corticosteroid dose with the aim to rapidly discontinue; discontinuing immunomodulating drugs; extensive surgical debridement to remove all necrotic material; antifungal therapy (e.g., amphotericin-B for initial therapy, followed by posaconazole or isavuconazole maintenance therapy or salvage therapy) for 4 to 6 weeks; and appropriate supportive care and monitoring. Patients should be under the care of a multidisciplinary team that includes an infectious disease specialist; an intensivist; a neurologist; a dentist; an ophthalmologist; an ear, nose, and throat specialist; and a surgeon.[1237] [1234]

- **Prevention:** prevention involves controlling hyperglycemia; monitoring blood glucose level in COVID-19 patients after discharge (whether or not they are diabetic); and judicious use of corticosteroids, antibiotics, and antifungals.[1234]
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<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>Complications: rare cases of pulmonary artery pseudoaneurysm have been reported with COVID-19-associated pulmonary mucormycosis.[1238]</td>
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<tr>
<td>Prognosis: overall mortality in India (36.5%) was less than that for globally reported cases (61.9%), likely due to the predominance of rhino-orbital mucormycosis in India.[1230] A significant proportion of survivors had life-changing morbidities (e.g., vision loss).[1228]</td>
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<tr>
<td>candidemia</td>
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<td>The overall incidence of candidemia ranges from 0.7% to 23.5%, with most cases occurring in the intensive care unit in mechanically ventilated patients.[1239] Cases of candidemia due to <em>Candida auris</em>, an emerging multidrug-resistant pathogen, have been reported.[1240] Reasons for the increased incidence in this population are poorly understood; however, patients are exposed to multiple risk factors for candidemia including corticosteroid therapy, immunosuppressive therapy, antibiotics, and long stays in the intensive care unit. A high mortality rate has been reported.[1241]</td>
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<tr>
<td>pancreatic injury</td>
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<td>Mild pancreatic injury (defined as elevated serum amylase or lipase levels) has been reported in 17% of patients in one case series.[1242] It is unknown whether this is a direct viral effect or due to the harmful immune response that occurs in some patients. Patients had an increased risk of severe pancreatitis and necrotizing pancreatitis, and a longer length of hospital stay.[1243] Patients with acute pancreatitis had a high pooled mortality (18.5%) and significantly worse clinical outcomes.[1244] Prior history of pancreatitis does not appear to be a risk factor for pancreatic inflammation in patients with COVID-19.[1245] A causal relationship between SARS-CoV-2 infection and acute pancreatitis has not been established.[1246]</td>
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<tr>
<td>immune thrombocytopenia</td>
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<td>Immune thrombocytopenia has been reported rarely. The majority of cases were in patients &gt;50 years of age, with only 7% of cases reported in children. The majority of cases were in patients with moderate to severe COVID-19; however, 7% of cases were in asymptomatic COVID-19 patients. Onset occurred in 20% of cases 3 weeks after the onset of COVID-19 symptoms, with most cases reported after clinical recovery. Severe life-threatening bleeding was uncommon. Treatment involved the use of corticosteroids, intravenous immune globulin, and thrombopoietin-receptor agonists.[1247]</td>
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<tr>
<td>thyroid disorders</td>
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<td>Subacute thyroiditis is a thyroid disease of viral or post-viral origin. Emerging evidence suggests that infection with SARS-CoV-2 may trigger subacute thyroiditis. A review of 21 cases found a female predominance, with the mean number of days between the start of COVID-19 illness and the appearance of symptoms of subacute thyroiditis being 25 days. Infection had resolved in the majority of patients before the onset of subacute thyroiditis symptoms. Fever and neck pain were the most common presenting complaints. Symptoms resolved in all patients after treatment; however, 5 patients reported having hypothyroid illness on follow-up.[1248] COVID-19 may also cause autoimmune thyroid disease or exacerbate underlying thyroid disease in remission. Cases of Grave disease, Hashimoto thyroiditis, and postpartum thyroiditis have been reported.[1249]</td>
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<tr>
<td>gastrointestinal complications</td>
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<td>Critically ill patients may develop gastrointestinal complications; however, it is unclear whether this is a manifestation of critical illness in general, or whether it is specific to COVID-19. One study found that patients with COVID-19 were more likely to develop gastrointestinal complications compared with those without COVID-19, specifically transaminitis, severe ileus, and mesenteric ischemia.[1250] In patients with acute mesenteric ischemia, small-bowel ischemia was the most prevalent finding on abdominal computed</td>
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## Complications

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<tr>
<td>tomography, followed by ischemic colitis. Nonocclusive mesenteric ischemia was the most common pattern of bowel involvement.</td>
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<tr>
<td>Macrovacular arterial/venous thrombosis has been identified in almost 50% of patients with bowel ischemia. Overall mortality in COVID-19 patients with gastrointestinal ischemia and radiologically evident mesenteric thrombotic occlusion was 38.7% and 40%, retrospectively.</td>
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<tr>
<td>Patients may have an increased risk of gastrointestinal bleeding compared with the general population; however, evidence is limited. The overall gastrointestinal bleeding rate has been reported to be 2%.</td>
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### Acute hair loss

Acute telogen effluvium, a type of diffuse hair loss, has been reported in patients recovering from infection. The median age of patients was 44 years, and most patients were female. The mean duration from COVID-19 symptom onset to the appearance of telogen effluvium was 74 days. Most patients recovered; however, a minority of patients had persistent hair fall. Stress may be a contributing factor.

### Parosmia

Parosmia (misperception of an odor) is a late-onset symptom that may develop approximately 3 months after infection. It may occur without any preceding apparent smell loss, or it may follow a short recovery period from initial anosmia. There are no effective, evidence-based treatments available; however, the patient should be offered useful tips on living with parosmia until recovery.

## Prognosis

### Mortality

The leading cause of death is respiratory failure from acute respiratory distress syndrome (ARDS).

- The overall pooled mortality rate from ARDS in COVID-19 patients is 39%; however, this varies significantly between countries (e.g., China 69%, Iran 28%, France 19%, Germany 13%).
- There is no evidence to suggest worse outcomes (i.e., mechanical ventilator-free days, length of stay in intensive care unit or hospital, or mortality) for patients with COVID-19-related ARDS compared with the general ARDS population.
- Risk factors for respiratory failure include older age, male sex, cardiovascular disease, laboratory markers (such as lactate dehydrogenase, lymphocyte count, and C-reactive protein), and high viral load on admission.
- Other common causes of death include sepsis or septic shock, sepsis-related multiorgan failure, bacterial or viral coinfections, venous thromboembolism, and cardiac failure.

Mortality rate depends on age and the presence of underlying medical conditions.

- People <65 years of age have a very small risk of death even in pandemic epicenters, and deaths in people <65 years of age without any underlying conditions is rare.
Deaths in children and young people are rare. According to preprint (not peer reviewed) data from the first pandemic year in England, 25 children and young people died, equivalent to an infection fatality rate of 5 per 100,000 and a mortality rate of 2 per million. This indicates that >99.995% of children recover from infection. The children who died were mainly >10 years of age and of Asian and Black ethnicity.[1023]

Approximately 99% of patients who died of COVID-19 had at least one underlying health condition in a US cohort study. The strongest risk factors for death were obesity, anxiety and fear-related disorders, and diabetes, as well as the total number of underlying conditions.[152]

Mortality rates are high in critically ill patients.

- In-hospital mortality decreased from 32.3% to 16.4% between March and August 2020 in a UK cohort study of over 80,000 patients. Mortality declined in all age groups, in all ethnic groups, in men and women, and in patients with and without comorbidities, over and above contributions from declining illness severity.[1025] Adjusted in-hospital mortality rates declined during the early part of the first wave in the UK and this was largely maintained during the second wave of the pandemic.[1026]

- Mortality rates decreased sharply in the US over the first 6 months of the pandemic.[1027] [1028] In-hospital mortality decreased from 10.6% to 9.3% between March and November 2020 in one US cohort study of over 500,000 patients across 209 acute care hospitals.[1029] Among patients with critical illness admitted to an intensive care unit at an academic health system in the US, the mortality rate decreased from 43.5% to 19.2% over the study period.[1030]

- This may reflect the impact of changes in hospital strategy and clinical processes, and better adherence to evidence-based standard of care therapies for critical illness over time, such as use of corticosteroids, high-flow nasal oxygen to avert intubation, prone positioning, and decreased use of mechanical ventilation. Further studies are needed to confirm these results and investigate causal mechanisms.

Infection fatality rate (IFR)

- Defined as the proportion of deaths among all infected individuals including confirmed cases, undiagnosed cases (e.g., asymptomatic or mildly symptomatic cases), and unreported cases. The IFR gives a more accurate picture of the lethality of a disease compared with the case fatality rate.
- It has been estimated that approximately 1.5 to 2 billion infections have occurred globally as of February 2021, with an estimated overall IFR of 0.15%. There are substantial differences in IFR and infection spread across continents, countries, and locations.[1031] Emerging preprint (not peer reviewed) data suggests that the median IFR in community-dwelling people ages ≥70 years was 2.9% (4.9% in people ages ≥70 years overall), but was much lower at younger ages (median 0.0013%, 0.0088%, 0.021%, 0.042%, 0.14%, and 0.65%, at 0-19, 20-29, 30-39, 40-49, 50-59, and 60-69 years respectively).[1032]
- The US Centers for Disease Control and Prevention’s current best estimate of the IFR, according to age:[91]
  - 0 to 17 years – 0.002%
  - 18 to 49 years – 0.05%
  - 50 to 64 years – 0.6%
  - ≥65 years – 9%.
- Based on these figures, the overall IFR for people <65 years of age is approximately 0.2%.
- Among people on board the Diamond Princess cruise ship, a unique situation where an accurate assessment of the IFR in a quarantined population can be made, the IFR was 0.85%. However, all
deaths occurred in patients >70 years of age, and the rate in a younger, healthier population would be much lower.[1033]

- These estimates have limitations and are likely to change as more data emerge over the course of the pandemic, especially in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.

Case fatality rate (CFR)

- Defined as the total number of deaths reported divided by the total number of detected cases reported. CFR is subject to selection bias as more severe/hospitalized cases are likely to be tested. CFR is a dynamic estimate that changes with time, population, socioeconomic factors, and mitigation measures.[1034]

- The World Health Organization's current estimate of the global CFR is 1.2% (as of 8 May 2022).[1035] CFR varies considerably between countries. The pooled CFR in the general population in a systematic review and meta-analysis was 1%.[1036] This is much lower than the reported CFR of severe acute respiratory syndrome coronavirus (SARS), which was 10%, and Middle East respiratory syndrome (MERS), which was 37%.[47]

- CFR increases with age.
  - In the US, the majority of deaths were in patients ages ≥65 years. The CFR was highest among patients ages ≥85 years (10% to 27%), followed by those ages 65 to 84 years (3% to 11%), then those ages 55 to 64 years (1% to 3%), and finally those ages 20 to 54 years (<1%).[25]
  - In China, the majority of deaths were in patients ages ≥60 years.[23] The CFR was highest among patients ages ≥80 years (13.4%), followed by those ages 60 to 79 years (6.4%), and then those ages <60 years (0.32%).[1037]
  - In Italy, the CFR was highest among patients ages ≥80 years (52.5%), followed by those ages 70 to 79 years (35.5%), and then those ages 60 to 69 years (8.5%).[1038]
  - Deaths are rare in children.[25] [31] In one study, 70% of deaths occurred in those ages 10 to 20 years, 20% in those ages 1 to 9 years, and 10% in children under 1 year of age.[1039]

- CFR increases with the presence of comorbidities.
  - In China, the majority of deaths were in patients who had preexisting underlying health conditions (10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6% for hypertension, and 5.6% for cancer).[23]

- CFR increases with disease severity.
  - The pooled CFR in hospitalized patients was 13%. [1036] The CFR is highest in patients with critical disease, ranging from 26% to 67% in studies.[23] [1040] [1041]

Limitations of IFR/CFR

- Estimating the IFR and CFR in the early stages of a pandemic is subject to considerable uncertainties and estimates are likely to change as more data emerges. Rates tend to be high at the start of a pandemic and then trend downwards as more data becomes available.[1042]
- There is currently no set case definition of a confirmed case, and case definitions vary. A positive polymerase chain reaction (PCR) result is sometimes the only criterion for a case to be recognized; however, a positive PCR test does not necessarily equal a diagnosis of COVID-19, or mean that a person is infected or infectious.[1043] [1044]
- The number of deaths reported on a particular day may not accurately reflect the number of deaths from the previous day due to delays associated with reporting deaths. This makes it difficult to know whether deaths are falling over time in the short term.[1045]
- Patients who die "with" COVID-19 and patients who die "from" COVID-19 may be counted towards the death toll in some countries. For example, in Italy only 12% of death certificates reported direct causality from COVID-19, while 88% of patients who died had at least one comorbidity.[1042] [1046]
Prognostic factors

Prognostic factors that have been associated with increased risk of severe disease, hospitalization or intensive care unit admission, poor outcomes, and mortality include:[1047] [1048] [1049] [1050] [1051] [1052] [1053]

- Patient factors
  - Increasing age
  - Male sex
  - Obesity
  - Smoking history
  - Blood type A
  - Frailty
- Presence of comorbidities
  - Hypertension
  - Cardiovascular disease
  - Cerebrovascular disease
  - Peripheral artery disease
  - Dementia
  - Diabetes
  - Chronic respiratory disease (e.g., COPD, obstructive sleep apnea)
  - Active malignancy
  - Immunosuppression
  - Chronic kidney or liver disease
  - Rheumatologic disease
  - Bacterial or fungal coinfection
- Symptoms/signs
  - Myalgia
  - Pharyngalgia
  - Sputum production
  - Chills
  - Nausea
  - Dyspnea
  - Chest tightness
  - Dizziness
  - Headache
  - Hemoptysis
  - Tachypnea
  - Hypoxemia
  - Respiratory failure
  - Hypotension
  - Tachycardia
- Complications
  - Shock
Coronavirus disease 2019 (COVID-19) Follow up

• Acute infection or sepsis
• Acute kidney, liver, or cardiac injury
• Acute respiratory distress syndrome
• Venous thromboembolism
• Arrhythmias
• Heart failure

• Investigations

• Lymphopenia
• Leukocytosis
• Neutrophilia
• Thrombocytopenia
• Hypoalbuminemia
• Liver or kidney impairment
• Elevated inflammatory markers (e.g., C-reactive protein, procalcitonin, ferritin, erythrocyte sedimentation rate, tumor necrosis factor-alpha, interferon gamma, interleukins, lactate dehydrogenase)
• Elevated creatine kinase
• Elevated cardiac markers
• Elevated D-dimer
• PaO₂/FiO₂ ≤200 mmHg
• Bilateral pneumonia on chest imaging
• Consolidative infiltrate or pleural effusion on chest imaging
• High sequential organ failure assessment (SOFA) score.

The most common underlying diseases in deceased patients were hypertension, diabetes, and cardiovascular diseases.[1054]

In children and adolescents, congenital heart disease, chronic pulmonary disease, neurologic diseases, obesity, multisystem inflammatory syndrome, shortness of breath, acute respiratory distress syndrome, acute kidney injury, gastrointestinal symptoms, and elevated C-reactive protein and D-dimer have been associated with unfavorable prognosis.[1055]

Hospital readmission

Approximately 10% of recovered patients require hospital readmission during the first year after discharge, based on very low-quality evidence. Most hospital readmissions occur within 30 days of discharge. Higher readmission rates have been reported in patients with underlying diseases, but the current evidence is contradictory and comes from studies with a low level of evidence. Higher readmission rates have also been reported in developed countries compared with developing countries, possibly due to the better access to medical services and the higher medical benefits provided in developed countries. The prevalence of post-discharge all-cause mortality of recovered patients was 7.87% within 1 year of discharge.[1056]

Persistent infections have been reported in immunocompromised people.[1057]

The risk of severe post-acute complications in patients who were not admitted to hospital for the primary infection appears to be low. However, they may be at slightly increased risk of venous thromboembolism, dyspnea, and initiating bronchodilator or triptan therapy compared with people who tested negative for SARS-CoV-2. These patients visited their general practitioner and outpatient hospital clinics more often after the primary infection than those who tested negative, which may indicate persistent symptoms that do not lead to specific drug treatment or hospital admission.[1058]
Reinfection

Reinfection refers to a new infection following previous confirmed infection (i.e., severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] real-time reverse transcription polymerase chain reaction [RT-PCR] positive), and is distinct from persistent infection and relapse. There is currently no standard case definition for SARS-CoV-2 reinfection.[1059]

There is limited information about reinfection.

- Recurrent RT-PCR positivity in patients 1 to 60 days after recovery ranges between 7% to 23% in studies, with an estimated pooled rate of 12%.\[1060\] Patients with longer initial illness and younger age were more likely to experience recurrent RT-PCR positivity, while those with severe disease, diabetes, and a low lymphocyte count were less likely.\[1061\] It is currently unclear whether this is due to reinfection; whether it is due to factors such as the type of specimen collection and technical errors associated with swab testing, infection by mutated SARS-CoV-2, or persistent viral shedding; or whether the test result was a false-negative at the time of discharge.\[1062\]
- Studies have repeatedly reported positive RT-PCR tests for up to 90 days after initial infection; therefore, it is most likely that these cases are actually protracted initial infections. It is important to note that although persistent viral shedding has been reported for up to 90 days after the onset of infection, replication-competent virus has not been identified 10 to 20 days after the onset of symptoms (depending on disease severity).\[1063\] A cohort study of 200 patients with past infection found that despite persistent pharyngeal RT-PCR positivity for up to 90 days after recovery, transmission to close contacts was not observed, indicating that these patients are not contagious at the post-symptomatic stage of infection.\[1064\]

Cases of reinfection are rare.

- The rate of reinfection is relatively low. A systematic review and meta-analysis found the pooled reinfection rate to be 0.65%. The reinfection rate was higher in high-risk populations (1.6%), and the rate of symptomatic reinfection was lower (0.4%).\[1065\]
- Across 18 studies, the reinfection risk ranged from 0% to 2.2%, and previous infection reduced the risk for reinfection by 87%. Protection remained above 80% for at least 7 months, but no study has followed patients after the emergence of the Delta or Omicron variants.\[1066\]

Consider reinfection in the following circumstances:\[1059\]

- A repeat positive RT-PCR test 90 days or more after a previous positive RT-PCR test
- New symptoms in a patient with previous RT-PCR-positive infection after apparent full recovery (i.e., resolution of previous symptoms) and a repeat positive RT-PCR test (including within 90 days after a previous positive RT-PCR test).

Diagnosis

- A compatible clinical presentation together with diagnostic evidence (such as a low RT-PCR cycle threshold value) may be sufficient to diagnose reinfection. However, the diagnosis should be made in conjunction with an infectious disease specialist following a risk assessment that involves reviewing available clinical, diagnostic, and epidemiologic information to inform whether reinfection is likely. Confirmation of reinfection should be obtained through whole genome sequencing of paired specimens, if available.\[1059\]
- Overall, 68.8% of patients with reinfection had similar disease severity as the initial episode, 18.8% had worse symptoms, and 12.5% had milder symptoms.\[1067\]

Management

- Manage patients with suspected reinfection as if they are infectious, as for a new or first infection. Advise the patient to self-isolate pending further investigation and clinical risk assessment. It is important to note that illness due to reinfection may not necessarily follow the same clinical course as the previous episode.\[1059\]
Immunity

The immune response to SARS-CoV-2 is not yet fully understood, but involves both cell-mediated and antibody-mediated immunity.

Adaptive immunity is thought to occur within the first 7 to 10 days of infection. A robust memory B-cell and plasmablast response is detected early in infection, with secretion of immunoglobulin A (IgA) and IgM antibodies by day 5 to 7, and IgG by day 7 to 10 from the onset of symptoms. T cells are simultaneously activated in the first week of infection and SARS-CoV-2-specific memory CD4+ and CD8+ T cells peak within 2 weeks. Antibody and T-cell response differ among individuals, and depend on age and disease severity.[1068]

Antibody-mediated immunity

- Approximately 85% to 99% of infected people develop detectable neutralizing antibodies within 4 weeks following natural infection. However, this varies depending on disease severity, study setting, time since infection, and method used to measure antibodies.[1069] [1070]
- Moderate-strength evidence suggests that most adults develop detectable levels of IgM and IgG antibodies after infection. IgM levels peak early in the disease course at approximately 20 days and then decline. IgG levels peak later at approximately 25 days after symptom onset and may remain detectable for at least 120 days. Most adults generate neutralizing antibodies, which may persist for several months. Some adults do not develop antibodies after infection; the reasons for this are unclear.[1071]
- Maternal IgG antibodies to SARS-CoV-2 have been found to transfer across the placenta after infection in pregnant women.[1072]
- Extreme-aged (some over 100 years), frail residents of a long-term care facility have been found to elicit a robust immune response that was capable of neutralizing the SARS-CoV-2 virus.[1073]
- There were some early studies that suggested asymptomatic people may have a weaker antibody response to infection; however, this has not been confirmed.[1074]
- Current evidence suggests that the immune responses remain robust and protective against reinfection in most people for at least 10 months after infection.[1075] [1076] A cross-sectional study of unvaccinated adults found evidence of natural immunity up to 20 months after infection, although it is unclear how antibody levels correlate with future protection, particularly with emerging variants.[1077]
- Some SARS-CoV-2 variants with key changes in the spike protein have a reduced susceptibility to neutralization by antibodies. However, cellular immunity elicited by natural infection also targets other viral proteins, which tend to be more conserved across variants than the spike protein.[1069]

Cell-mediated immunity

- The majority of people develop a strong and broad T-cell response with both CD4+ and CD8+ T cells, and some have a memory phenotype.[1078]
- CD4+ and CD8+ T cells declined with a half-life of 3 to 5 months in adults who recovered, and are likely to be present in most adults at least 6 to 8 months after primary infection.[1079] [1080]
- Emerging data suggest that T-cell responses are largely unaffected by SARS-CoV-2 variants.[1081] [1082]

Evidence suggests that natural infection with SARS-CoV-2 is likely to confer high protective immunity against reinfection.

- Robust antibody and T-cell immunity against SARS-CoV-2 is present in the majority of recovered patients 12 months after moderate to critical infection. Neutralizing antibodies diminished between 6 and 12 months after infection, mostly in older people and critical patients. However, memory T-cells retained the ability to mediate cellular immunity in patients who had lost their neutralizing antibody responses. Memory T-cell responses to the original SARS-CoV-2 strain were not disrupted by new variants.[1083] Convalescent critically ill patients consistently generated substantial adaptive and humoral immune responses against SARS-CoV-2 for more than 1 year after hospital discharge.[1084]
Follow up

- Meta-analyses have found a high (84% to 87%) level of protection after infection that persisted for at least 1 year.[1085] [1086]
- A UK Health Security Agency study found that naturally acquired immunity, as a result of past infection, provides 84% protection against reinfection compared with people who have not had the disease previously, and protection appeared to last for at least 7 months.[1087]
- Similarly, a population-level observational study among 4 million PCR-tested people in Denmark found protection against repeat infection in the population to be 80% or higher in those younger than 65 years of age, and 47% in those older than 65 years of age. There was no evidence of waning protection over time.[1088]
- A registry-based study from Sweden found that natural immunity was associated with a 95% lower risk of reinfection and an 87% lower risk of hospitalization compared with no immunity, for up to 20 months. Vaccination appeared to further decrease the risk of both outcomes for up to 9 months, although the differences in absolute numbers were small.[1089]
- A cohort study across six US states found that unvaccinated people with prior symptomatic COVID-19 had an 85% lower risk of acquiring COVID-19 than unvaccinated individuals without prior COVID-19, and suggests that natural immunity was associated with similar protection against both mild and severe disease.[1090]
- An observational study from Lombardy, Italy, found that natural immunity appears to confer a protective effect for at least 1 year; however, the study ended before SARS-CoV-2 variants began to spread, and it is unknown how well natural immunity to the wild-type virus will protect against these variants.[1091]

Preexisting immunity to SARS-CoV-2

- Testing of blood samples taken before the COVID-19 pandemic has shown that some people already have immune cells that recognize SARS-CoV-2. Studies have reported T-cell reactivity against SARS-CoV-2 in 20% to 50% of people with no known exposure to the virus.[1092] Approximately 5% of uninfected adults and 62% of uninfected children aged 6 to 16 years had antibodies that recognize SARS-CoV-2 in one study.[1093]
- This may be a consequence of true immune memory derived in part from previous infection with common cold coronaviruses, or from other unknown animal coronaviruses. However, further research into whether there is preexisting immunity to SARS-CoV-2 in the human population is required.

Natural versus vaccine-induced immunity

- Protection after natural infection appears to be comparable to that estimated for vaccine efficacy.[1065]
- Emerging evidence suggests that natural immunity may confer at least equal or longer-lasting and stronger protection against infection, symptomatic disease, and hospitalization caused by the Delta variant, or other variants of concern, compared with vaccine-induced immunity.[1094] [1095]
- During the Delta wave in the US (between May and November 2021), people who were previously infected, both with or without prior vaccination, had the greatest protection from infection. By early October, people who survived a previous infection had lower case rates than persons who were vaccinated alone.[1096]

The data presented here is from before the emergence of the Omicron variant (see the Classification section for more information on Omicron).
# Diagnostic guidelines

## International

**Overview of testing for SARS-CoV-2, the virus that causes COVID-19**


*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2022

**Interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 (COVID-19) pandemic**


*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2022

**COVID-19 testing guidance**


*Published by:* American Academy of Pediatrics  
*Last published:* 2022

**Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: antigen testing**


*Published by:* Infectious Diseases Society of America  
*Last published:* 2021

**Infectious Diseases Society of America guidelines on infection prevention for healthcare personnel caring for patients with suspected or known COVID-19**


*Published by:* Infectious Diseases Society of America  
*Last published:* 2021

**Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: molecular diagnostic testing**


*Published by:* Infectious Diseases Society of America  
*Last published:* 2020

**Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: serologic testing**


*Published by:* Infectious Diseases Society of America  
*Last published:* 2020

**Use of SARS-CoV-2 antigen-detection rapid diagnostic tests for COVID-19 self-testing**


*Published by:* World Health Organization  
*Last published:* 2022
# International


**Published by:** World Health Organization  
**Last published:** 2022


**Published by:** World Health Organization  
**Last published:** 2021

**Diagnostic testing for SARS-CoV-2: interim guidance** ([https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2](https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2)) [539]

**Published by:** World Health Organization  
**Last published:** 2020


**Published by:** World Health Organization  
**Last published:** 2020


**Published by:** UK Health Security Agency; NHS England; Public Health Wales; Public Health Agency (Northern Ireland)  
**Last published:** 2022

**Assessment of COVID-19 in primary care** ([https://www.sign.ac.uk/our-guidelines](https://www.sign.ac.uk/our-guidelines)) [791]

**Published by:** Scottish Intercollegiate Guidelines Network  
**Last published:** 2022


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**Published by:** Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team; Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care  
**Last published:** 2020


**Published by:** Peking Union Medical College Hospital  
**Last published:** 2020
## Treatment guidelines

### International

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**Home care for patients with suspected or confirmed COVID-19 and management of their contacts: interim guidance**

*Published by: World Health Organization*  
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**BMJ's coronavirus (covid-19) hub**

*Published by: BMJ*  
*Last published: 2022*

**COVID-19: the green book, chapter 14a**

*Published by: UK Health Security Agency*  
*Last published: 2022*

**Coronavirus (COVID-19) infection in pregnancy**

*Published by: Royal College of Obstetricians and Gynaecologists (UK)*  
*Last published: 2022*

**COVID-19 rapid guideline: managing COVID-19**

*Published by: National Institute for Health and Care Excellence (UK)*  
*Last published: 2022*

**Coronavirus specialty guides**

*Published by: NHS England*  
*Last published: 2022*

**COVID-19 rapid guideline: managing the long-term effects of COVID-19**

*Published by: National Institute for Health and Care Excellence (UK)*  
*Last published: 2021*

**Prevention and management of venous thromboembolism in COVID-19**

*Published by: Scottish Intercollegiate Guidelines Network*  
*Last published: 2021*

**Managing the long-term effects of COVID-19**

*Published by: Scottish Intercollegiate Guidelines Network*  
*Last published: 2021*

**COVID-19: guidance for health professionals**

*Published by: UK Health Security Agency*  
*Last published: 2021*

**Management of hospitalised adults with coronavirus disease-19 (COVID-19)**

*Published by: European Respiratory Society*  
*Last published: 2021*
### International

#### Clinical guidance for management of adult COVID-19 patients

- **Published by:** All India Institute Of Medical Sciences; Indian Council of Medical Research
- **Last published:** 2022

#### COVID-19 infection

- **Published by:** Japanese Association for Infectious Diseases
- **Last published:** 2022

#### Coronavirus disease 2019 (COVID-19)

- **Published by:** Department of Health Australia
- **Last published:** 2022

#### Handbook of COVID-19 prevention and treatment

- **Published by:** First Affiliated Hospital, Zhejiang University School of Medicine
- **Last published:** 2020

#### Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7)

- **Published by:** National Health Commission of the People's Republic of China; National Administration of Traditional Chinese Medicine of the People's Republic of China
- **Last published:** 2020

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- **Published by:** Peking Union Medical College Hospital
- **Last published:** 2020
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Coronavirus disease 2019 (COVID-19)

References


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Figure 1: Number of COVID-19 cases reported weekly by WHO Region, and global deaths, as of 8 May 2022

World Health Organization
Figure 2: Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically

Centers for Disease Control and Prevention
Figure 3: Multi-organ complications of COVID-19 and long COVID. The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor

BMJ. 2021;374:n1648
Figure 4: Virus replication cycle

BMJ. 2020;371:m3862
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Administration Information</th>
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</table>
| **Pfizer/BioNTech**    | **Primary series**: 5-11 years: 0.2 mL (10 mcg) IM; second dose 3 weeks later; third dose 4 weeks later in moderately or severely immunocompromised  
|                        | **Booster series**: Not currently recommended in this age group |
| **Pfizer/BioNTech**    | **Primary series**: ≥12 years: 0.3 mL (30 mcg) IM; second dose 3-8 weeks* later; third dose 4 weeks later in moderately or severely immunocompromised  
| (purple or grey cap)   | **Booster series**: ≥12 years: 0.3 mL (30 mcg) IM at least 5 months after primary series (3 months in moderately or severely immunocompromised); a second booster may be offered 4 months after the first booster** |
| **Moderna**            | **Primary series**: ≥18 years: 0.5 mL (100 mcg) IM; second dose 4-8 weeks* later; third dose 4 weeks later in moderately or severely immunocompromised  
| (red cap)              | **Booster series**: ≥18 years: 0.25 mL (50 mcg) IM at least 5 months after primary series (3 months in moderately or severely immunocompromised); a second booster may be offered 4 months after the first booster** |
| **Janssen**            | **Primary series**: ≥18 years: 0.5 mL IM as a single dose; second dose of an mRNA vaccine 4 weeks later in moderately or severely immunocompromised (use is limited to certain people)  
| (blue cap)             | **Booster series**: ≥18 years: 0.5 mL IM at least 2 months after primary series; a second booster may be offered 4 months after the first booster** |

*An 8-week interval may be optimal for some people (e.g., males ages 12 to 39 years due to risk of myocarditis associated with mRNA vaccines).

**A second booster may be considered in some people. See Interim clinical considerations for use of COVID-19 vaccines currently approved or authorized in the United States for more detailed information (link above). Last updated: 12 May 2022*
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Common</th>
<th>Uncommon</th>
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<tbody>
<tr>
<td>Pfizer/BioNTech</td>
<td>injection-site reactions; fatigue; headache; myalgia; chills; arthralgia; fever; diarrhea; nausea/vomiting</td>
<td>malaise; lymphadenopathy; asthenia; decreased hepatitis; hyperhidrosis; lethargy; night sweats; myocarditis; pericarditis; anaphylaxis and other hypersensitivity reactions; pain in extremity (arm); facial paralysis</td>
</tr>
<tr>
<td>Moderna</td>
<td>injection-site reactions; fatigue; headache; myalgia; chills; arthralgia; nausea/vomiting; axillary swelling/tenderness; fever</td>
<td>lymphadenopathy; anaphylaxis and other hypersensitivity reactions; delayed injection-site reactions; facial paralysis; herpes zoster; face swelling (dermatologic fillers present); myocarditis; pericarditis; syncope</td>
</tr>
<tr>
<td>Janssen</td>
<td>injection-site reactions; fatigue; headache; myalgia; fever</td>
<td>diarrhea; nausea/vomiting; lymphadenopathy; anaphylaxis and other hypersensitivity reactions; pain in extremity (arm); thrombosis with thrombocytopenia; immune thrombocytopenia; myocarditis; pericarditis; tinnitus; Guillain-Barre syndrome; syncope; paresthesia; hypoesthesia; capillary leak syndrome; venous thromboembolism; seizures</td>
</tr>
</tbody>
</table>

*Figure 6: Adverse effects associated with vaccines authorized or approved in the US. Information is taken from the US prescribing information. Last updated: 12 May 2022*

*BMJ Best Practice editorial team; compiled using data from the US product information*
Figure 7: Transverse CT scans from a 32-year-old man, showing ground-glass opacity and consolidation of lower lobe of right lung near the pleura on day 1 after symptom onset (top panel), and bilateral ground-glass opacity and consolidation on day 7 after symptom onset

Xu XW et al. BMJ. 2020;368:m606
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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style
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