BMJ Best Practice

Coronavirus disease 2019 (COVID-19)

Straight to the point of care

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Summary

Coronavirus disease 2019 (COVID-19) is a potentially severe acute respiratory infection.

Respiratory transmission is the dominant mode of transmission, with proximity and ventilation being the key determinants of transmission risk. Transmission is more likely if contacts are exposed shortly before or after symptom onset in the index patient.

Patients may be minimally symptomatic or asymptomatic, while others may present with severe pneumonia or other complications.

People with comorbidities are at increased risk for severe disease, and the more comorbidities, the greater the risk. Hypertension, obesity, and diabetes are the most prevalent comorbidities.

Diagnosis is confirmed with real-time reverse transcription polymerase chain reaction (RT-PCR); rapid antigen tests may be recommended in certain circumstances.

Management depends on disease severity and focuses on infection prevention and control measures, symptom management, prevention of disease progression (e.g., antiviral treatment), optimized supportive care, and organ support in severe or critical illness.

Numerous vaccines are available globally for prevention.

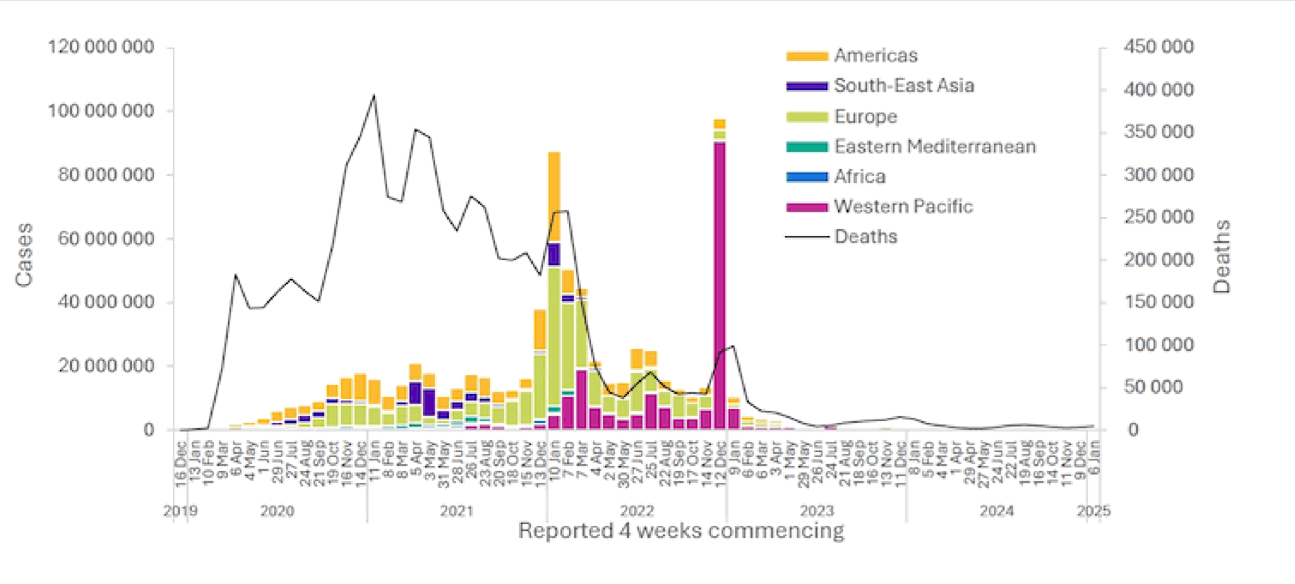
Definition

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. Complications of severe disease include, but are not limited to, multi-organ failure, septic shock, and venous thromboembolism.

Epidemiology

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 escalated and rapidly spread around the world, with the WHO first declaring a public health emergency of international concern (PHEIC) on 30 January 2020, and then formally declaring it a pandemic on 11 March 2020. The WHO declared that COVID-19 no longer constitutes a PHEIC in May 2023.

Cases have been reported across all continents since the beginning of the pandemic, with over 777 million confirmed cases and over 7 million deaths reported globally.[17]



Number of COVID-19 cases reported weekly by WHO Region, and global deaths, as of 2 February 2025

World Health Organization

Updated case counts are available from the WHO and the Centers for Disease Control and Prevention (CDC):

- [WHO: COVID-19 dashboard] (https://data.who.int/dashboards/covid19/cases?n=c)
- [CDC: surveillance and data analytics] (https://www.cdc.gov/covid/php/surveillance/index.html)

Older people age ≥70 years and males are at increased risk for infection and severe disease.[18] Adolescents appear to have similar susceptibility to infection as adults, and children have a lower susceptibility. However, evidence is conflicting.[19] [20] Unlike adults, children do not seem to be at higher risk for severe disease based on age or sex.[21] Variants may have spread more effectively and rapidly among young children compared with the wild-type virus, although hospitalization rates decreased.[22] [23]

The incidence of infection in healthcare workers ranged from 0% to 49.6%, and the prevalence of seropositivity ranged from 1.6% to 31.6%. There was no association between age, sex, or healthcare worker role (i.e., nurse versus physician) and the risk for infection, based on moderate-certainty evidence. There was an association between black race or Hispanic ethnicity and increased risk for infection in healthcare workers compared with white race or non-Hispanic ethnicity, based on moderate-certainty evidence. There was an association between use of personal protective equipment and decreased risk for infection, based on moderate-certainty evidence.[24] [25]

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.[26]
- 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.[27] [28]
- See the Classification section for information on SARS-CoV-2 variants.

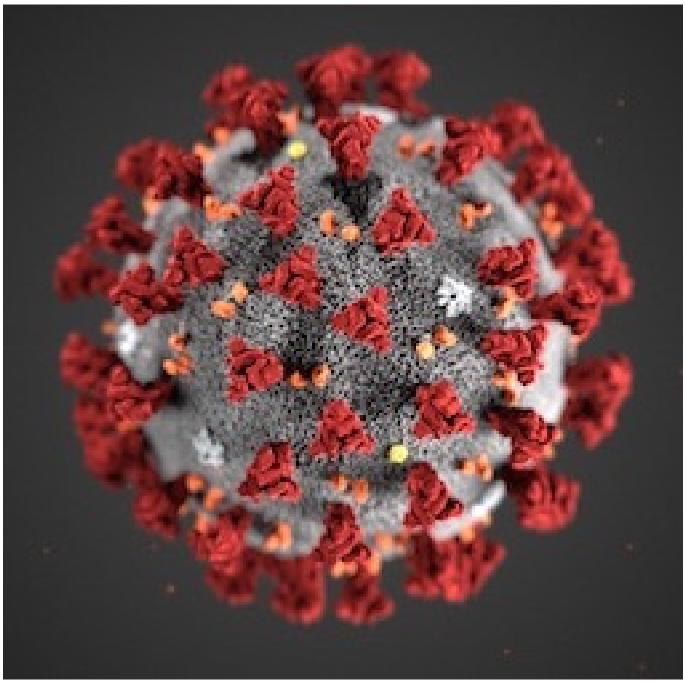


Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically

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.[29] [30] [31] 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.[31] Other studies suggest that the virus may have emerged earlier than previously thought in other countries.[32] [33]

- A zoonotic origin has not been confirmed. Some studies suggested 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 humans through one or several intermediary animal species.[34]
- An independent assessment of the origins of SARS-CoV-2 concluded that there are data gaps that preclude determining how the virus initially entered the human population with any certainty.[35]

Transmission dynamics

- Respiratory transmission is the dominant mode of transmission, with proximity and ventilation being the key determinants of transmission risk.[36] 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.[37]
- 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).[37] [38] A detailed investigation of these clusters suggests that droplet and fomite transmission could also explain the transmission in these reports.[37] 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.[39] The risk of transmission is much lower outdoors compared with indoors, with a limited number of studies estimating a transmission rate of <1%.[40] [41] 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.[42]
- 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.[36] 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.[43] Replication-competent virus is more likely to be identified when polymerase chain reaction cycle threshold for clinical specimens from infected individuals is <30 (i.e., high viral load).[44]
- 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.[36]
- Transmission via other body fluids (including sexual transmission or bloodborne transmission) has not been reported.[36] [45] 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.[46] There are limited data about the transmission risk from organ donors. However, there appears to be a low risk of transmission with nonlung (i.e., kidney, liver, heart) organs from SARS-CoV-2-positive donors, irrespective of whether the donor is symptomatic at the time of procurement.[47]

- Perinatal (vertical) transmission occurs rarely and transplacental transmission has been documented. There is limited evidence on the extent of vertical transmission and its timing.[48] Further high-quality studies are required to establish whether perinatal transmission occurs.[49] 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.[50]
- 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.[51] Hospital-acquired infections accounted for approximately 11.3% of infections in the UK between February and August 2020 (rates as high as 25% were reported). 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%).[52] [53] 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.[54] The risk to healthcare workers performing or assisting with a tracheostomy appears to be low.[55]
- [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.
  - The risk of transmission to close contacts was higher if exposure occurred between -2 and 3 days from symptom onset in the index patient in one study. 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.[56]
  - The median duration of infectiousness in patients with mild disease in a real-world community setting (pre-Omicron variant) was approximately 5 days (range 3 to 7 days) in one study. Symptom onset was a median of 3 days before peak viral RNA and infectious viral load. Less than 25% of cases shed infectious virus before symptom onset. Two-thirds of cases were still infectious 5 days after symptom onset, and one third were still infectious at 7 days.[57]
- Onward transmission varies according to specific host and contact factors, and the nature of the exposure. Factors associated with increased transmission include:[58]
  - Environmental factors: indoors, poor ventilation, crowding, close proximity, shared facilities, cold ambient temperature, low humidity
  - Host factors: recently infected, high viral load, severe disease, age, presence of comorbidities, immunocompromised
  - Behavioral factors: singing/shouting, coughing/sneezing, hugging/kissing, mask etiquette, hand hygiene, duration of contact
  - Viral factors: changes in the viral genome linked to increased transmissibility.
- 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.[37]
- Presymptomatic transmission

    - Transmission may occur during the incubation period before symptom onset.
    - While there is evidence of transmission from presymptomatic people, there is limited evidence on how frequently this is likely to occur and estimated transmission rates are highly variable.[59] [60]
    - Only 7% of people exposed to a presymptomatic index case became infected in one systematic review.[61] After controlled experimental inoculation with SARS-CoV-2 virus, only 7% of virus emissions into the air and environment occurred before the first reported symptom, suggesting that presymptomatic transmission is responsible for a small fraction of infections.[62]
    - 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).[63] [64] [65] [66] [67] [68] 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.[69] [70] [71] [72] Only 1% of people exposed to an asymptomatic index case became infected in one systematic review, suggesting limited infectiousness.[61]
    - Evidence on the transmission dynamics associated with the Omicron variant is mixed, with some studies suggesting that symptomatic cases were more likely to transmit the infection compared with asymptomatic cases, and other studies showing no difference.[73]
    - Estimating the prevalence of asymptomatic cases in the population is difficult. One living systematic review and meta-analysis found that the interquartile range for the proportion of persistently asymptomatic cases was 14% to 50% across studies; however, heterogeneity was high so the study did not estimate a mean proportion of overall asymptomatic infections.[74] 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.[75] The pooled percentage of asymptomatic infections has been estimated to be 25.5% to 32.4% among patients infected with the Omicron variant.[76]
    - 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.[77]
    - 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.[20]

Superspreading events

- Superspreading 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.[78]

- Limited transmission has been reported in childcare, school, and university settings.[79] [80] 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%). Evidence suggests the overall infection attack rate and SARS-CoV-2 positivity rate in school settings are low.[81] [82] 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.[83] In one study, infection in close contacts in secondary schools and colleges in England was uncommon (approximately 2%).[84]
- 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.[85]

Viral transmission factors

- Incubation period
  - The mean incubation period has been estimated to be between 5 and 7 days, and may differ depending on the variant.[86] The mean incubation period has decreased gradually from the wild-type virus (5.2 days) to the Omicron variant (3.42 days). The overall pooled incubation period was 6.57 days (range 1.8 to 18.87 days), and was higher in older adults (7.43 days) and children (8.82 days).[87]
- Reproduction number (R_0)
  - A systematic review and analysis estimated the reproduction number to be 2.69 (based on published literature from January to August 2020). However, the R_0 differs depending on various factors.[88]
- 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.[89] However, the rate varied between contact settings with an estimated rate of 18.9% to 37.3% in household settings, 42% among residents in aged-care facilities, 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.[74] [90] [91] [92][93] [94] The rate in children and young people was higher in household settings compared with school settings.[95] The secondary attack rate in household settings due to transmission from a pediatric index case ranged from 0% to 75% across studies.[96] The secondary attack rate for the Omicron variant is higher compared with other SARS-CoV-2 variants.[93] [97]
- 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.[98] 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,

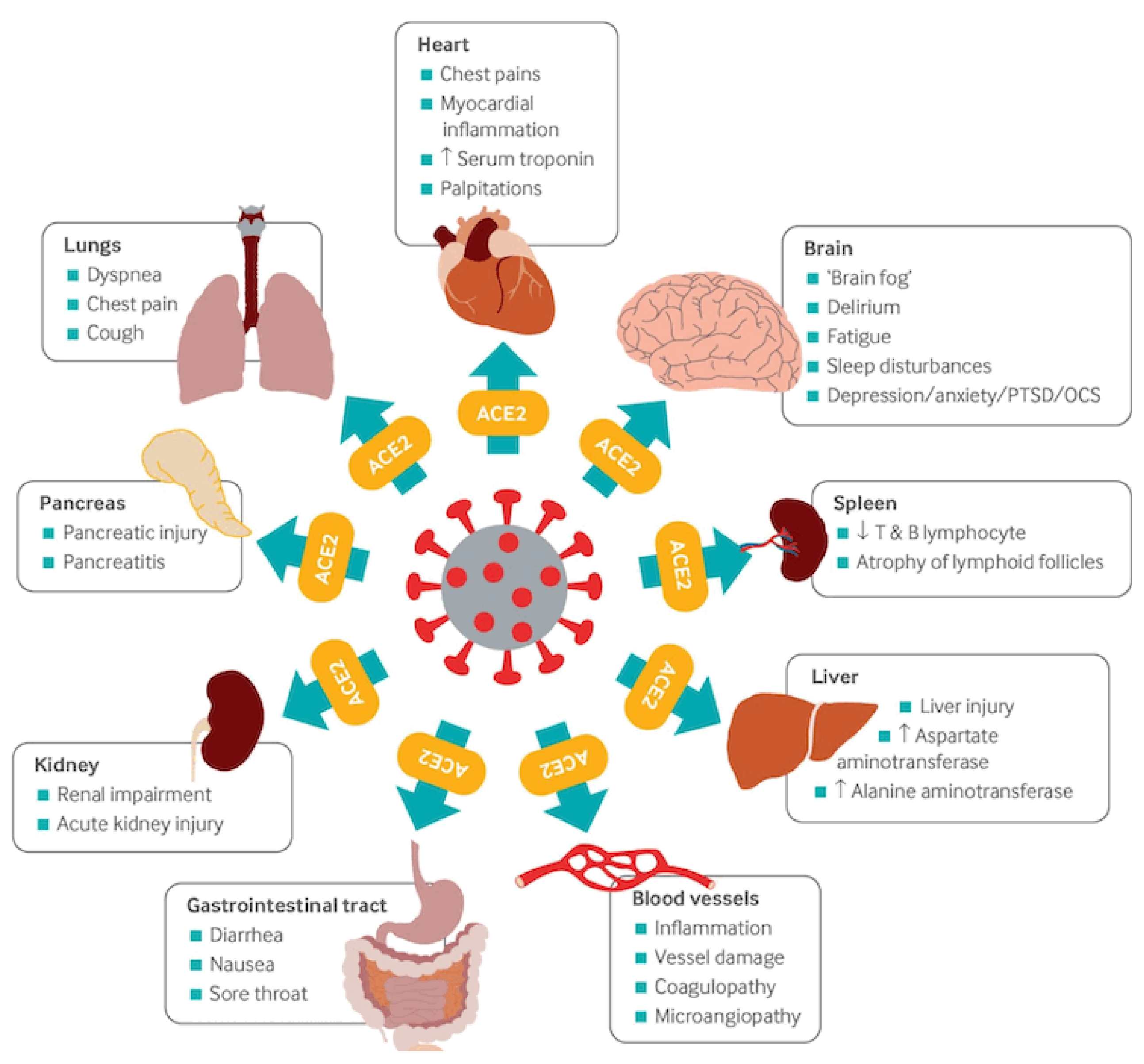
most studies demonstrate faster viral clearance among asymptomatic people compared with symptomatic people.[99]

- 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, in children compared with adults, and in patients with severe illness compared with those with nonsevere illness.[99] [100] Immunocompromised patients may shed for at least 2 months.[101] There are reports of super shedders who shed the virus for prolonged amounts of time (the longest was a case who tested positive for 505 days).[102] There is no convincing evidence that duration of viral shedding correlates with duration of infectivity.[103] 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.[36] Fully vaccinated people may have a shorter duration of viable shedding compared with partially vaccinated or unvaccinated people.[104]
  - The pooled duration of viable virus shedding was 5.2 days for the Omicron variant, with the duration being slightly higher in symptomatic patients compared with asymptomatic patients (although the difference was not significant).[105]

Pathophysiology

The exact pathophysiology is unknown, partly due to the scarcity of postmortem studies.[106] The pathophysiology resembles that of other coronavirus infections. However, some evidence indicates that COVID-19 has distinctive pathophysiological features that set it apart from respiratory failure of other origins.[107]

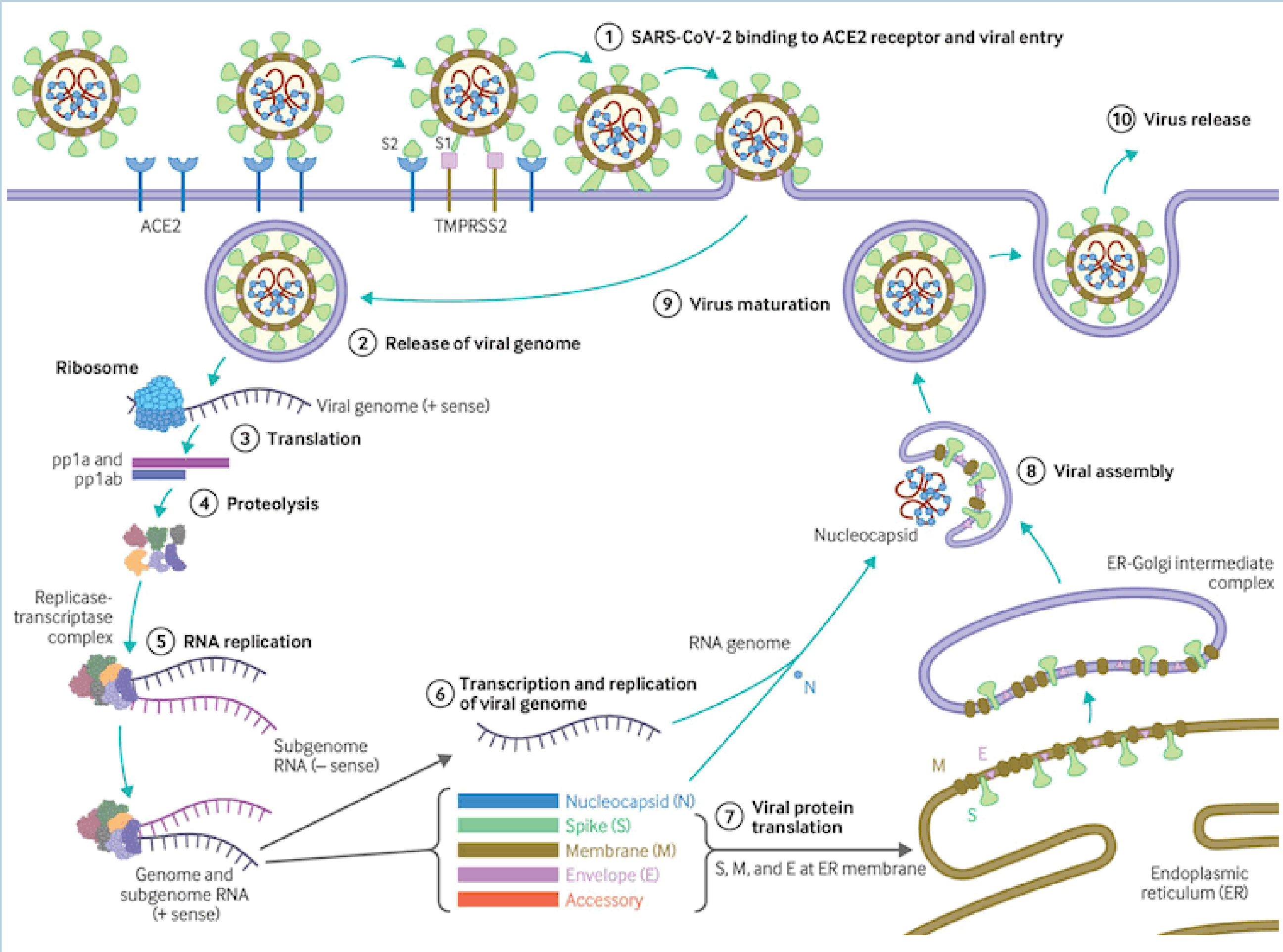
SARS-CoV-2 attaches to the angiotensin-converting enzyme-2 (ACE2) receptor on target host cells, followed by internalization and replication of the virus. ACE2 receptors are highly expressed in the upper and lower respiratory tract cells, but are also expressed in myocardial cells, renal epithelial cells, enterocytes, and endothelial cells in multiple organs, which may explain the extrapulmonary manifestations associated with the disease.[108] Viral RNA has been identified in many organs in postmortem studies.[106]



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.[109] 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.[110] This furin-like cleavage site does not appear to exist in other coronaviruses.[111] 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.[112] 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.[113] [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]



Virus replication cycle

BMJ. 2020;371:m3862

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.[106] [108] [116] The majority of findings in nonpulmonary organs were related to chronic diseases.[117] SARS-CoV-2-induced endotheliitis may play a role in both the respiratory and nonrespiratory manifestations.[118]

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.[119] Severe pulmonary disease is a consequence of fibrotic remodeling and secondary lobular microischemia, resulting in a distinctive form of fibrotic interstitial lung disease.[120]

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.[121]

Genetic factors may play a role in susceptibility to infection and disease severity; however, further research is required.[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.

SARS-CoV-2 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.

The WHO assigns simple labels for variants of concern using letters of the Greek alphabet. Previously, Greek labels were also used to name variants of interest, but this is no longer the case. This labeling does not replace existing scientific names (e.g., Pango, Nextstrain, GISAID), which continue to be used in research.[2]

Variant under monitoring

- The WHO defines a variant under monitoring as a variant with genetic changes that are suspected to affect virus characteristics and early signals of growth advantage relative to other circulating variants (e.g., growth advantage that can occur globally or in only one WHO region), but for which evidence of phenotypic or epidemiologic impact remains unclear, requiring enhanced monitoring and reassessment pending new evidence. If a variant has an unusually large number of mutations in known antigenic sites, but with very few sequences and it is not possible to estimate its relative growth advantage, such a variant can also be designated a variant under monitoring if there is also evidence of community transmission in two or more countries within a 2-4 week period.[3]

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, virulence, antibody evasion, susceptibility to therapeutics and detectability; and identified to have a growth advantage over other circulating variants in more than one WHO region with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.[3]

Variant of concern

- The WHO defines a variant of concern as a variant that meets the definition of a variant of interest (see above) and determined to be associated with a moderate or high level of confidence (through a risk assessment performed by WHO), meets at least one of the following criteria when compared with other variants:[3]
    - Detrimental change in clinical disease severity, or

- Change in epidemiology causing substantial impact on the ability of health systems to provide care to patients with COVID-19 or other illnesses and therefore requiring major public health interventions, or
- Significant decrease in the effectiveness of available vaccines in protecting against severe disease.

Former variants of concern

SARS-CoV-2 variants of concern are now extinct, with the current circulating variants of interest and variants under monitoring being the various Omicron subvariants (see below). Variants have sequentially replaced each other since the start of the pandemic, with the most successful variants being Alpha (B.1.1.7), Delta (B.1.617.2), and Omicron (B.1.1.529). Alpha and Delta emerged in late 2020, with Omicron emerging in late 2021. Beta (B.1.351) and Gamma (P.1) were also variants of concern.[4]

- The Alpha variant was more transmissible than the wild-type virus, and was 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. It was not associated with changes in the symptoms reported or their duration.[5] [6] [7] [8]
- The Delta variant was more transmissible than the wild-type virus and Alpha variant, and was associated with an increased risk of hospitalization (suggesting more severe disease) compared with contemporaneous Alpha and Beta cases. However, there was a high level of uncertainty in the findings. The crude case fatality rate was less than the Alpha variant.[9]

Omicron variant

The Omicron variant comprises the parental lineage B.1.1.529 and its descendent lineages (or subvariants) BA.1, BA.2, BA.3, BA.4, and BA.5, as well as their various sublineages. Omicron subvariants are currently in circulation.

The WHO considers the classification of Omicron sublineages independently as variants under monitoring, variants of interest, or variants of concern. Previously, Omicron sublineages were all classified as part of the Omicron variant of concern. This classification did not have the granularity needed to compare new descendent lineages with altered phenotypes to the Omicron parent lineages BA.1, BA.2, BA.3, BA4, and BA.5.[10]

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.[11] Cases were first reported in South Africa in November 2021. Omicron showed substantial growth advantage over Delta, and rapidly replaced Delta globally. The Omicron variant became the dominant variant in many countries, and accounted for over 98% of publicly available sequences since February 2022.[10]

Evidence suggests reduced disease severity and lower mortality for the Omicron variant compared with the Delta variant, after adjusting for the confounding effects of age, sex, ethnicity, prior infection, vaccination status, comorbidities, and effect of province and effect of public/private sector.[12] [13] The majority of deaths occurred in adults ages ≥65 years and patients with ≥3 underlying medical conditions.[14] Evidence from animal studies and ex vivo cultures of the human lower and upper respiratory tract suggests that Omicron does not infect cells deep in the lung as readily as it does cells in the upper airways.[15][16] Transmission, disease severity/hospitalization rate, and vaccine efficacy may differ depending on the specific

Omicron sublineage. Recent variants do not appear to cause more severe disease compared with previous variants.[2]

Several recombinant SARS-CoV-2 variants have been identified over the course of the pandemic, and the vast majority do not appear to confer any advantage to the virus.

Currently circulating variants

There are currently no circulating variants of concern, but there are variants of interest and variants under monitoring. Consult your local public health authority for the most current information on circulating variants in your area. The following resources are available:

- [WHO: tracking SARS-CoV-2 variants] (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants)
- [UKHSA: SARS-CoV-2 - genome sequence prevalence and growth rate] (https://www.gov.uk/government/publications/sars-cov-2-genome-sequence-prevalence-and-growth-rate)
- [CDC: variants and genomic surveillance] (https://www.cdc.gov/covid/php/variants/variants-and-genomic-surveillance.html)

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 with sickle cell disease presents 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 until her test results are available, and call her doctor if her symptoms get worse. Her test is confirmed to be positive for SARS-CoV-2 later that day. A clinician calls her to discuss treatment options given her increased risk of hospitalization.

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.

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 and follow local infection prevention and control guidelines.
- Suspect the diagnosis in patients with the following signs/symptoms: a new continuous cough, fever, altered sense of taste or smell, sore throat, fatigue, headache, dyspnea, myalgia, arthralgia, rhinorrhea, nasal congestion, sneezing, malaise, expectoration, or chest tightness/pain, particularly if the person has been in contact with a suspected or confirmed case. Patients may also present with gastrointestinal, cutaneous, or ocular symptoms.[435] [436]
- 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.[437] However, a rare multisystem inflammatory condition has been reported.[438]
- Order a real-time reverse transcription polymerase chain reaction (RT-PCR) to confirm the diagnosis. Upper and lower respiratory specimens are preferred.[439] Rapid antigen tests may be recommended in certain circumstances.[440] [441] [442]
- Order the following laboratory investigations in hospitalized patients: complete blood count, comprehensive metabolic panel, arterial blood gas, thyroid function tests, 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.[443] Consult local guidelines as imaging recommendations may vary.
- 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.

- 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.[444]
- Immediately isolate all suspected and confirmed cases and implement local infection prevention and control procedures.

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 settings, humanitarian settings) 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 determined by local health authorities based on 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]

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.

- The majority of patients have mild illness that does not warrant medical intervention or hospitalization, depending on the circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant.
- The pooled proportion of nonsevere illness in people infected with the Omicron variant was 98%, and the pooled proportion of asymptomatic infection was 25% (proportions varied depending on vaccination status).[445]

Common symptoms include:

- Fever
- Cough
- Fatigue
- Myalgia
- Arthralgia
- Dyspnea
- Altered sense of taste/smell
- Sore throat
- Headache
- Rhinorrhea
- Nasal congestion
- Sneezing
- Expectoration

Less common or uncommon symptoms include:

- Chest tightness/pain
- Malaise
- Dizziness

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- Confusion
- Delirium
- Gastrointestinal symptoms
- Cutaneous symptoms
- Ocular symptoms
- Hemoptysis
- Audio-vestibular symptoms
- Oral mucosal lesions

For more detailed information on signs and symptoms, see History and exam .

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 the presence of anosmia and/or ageusia may be useful as a red flag for diagnosis. Cough or fever may also increase the probability of diagnosis to an extent that is clinically relevant and should prompt further testing. Other symptoms increase the probability of the diagnosis to a much lesser extent.[446]

Signs and symptoms may differ in the context of circulating SARS-CoV-2 variants.

- Symptoms that characterize infection with the Omicron variant differ moderately from those that characterized infection with the Delta variant. There has been a shift towards predominantly upper respiratory tract symptoms with the Omicron variant and its subvariants.[447]
- The most common symptoms of Omicron infection according to data from the UK COVID Symptom Study were rhinorrhea, headache, fatigue, sneezing, and sore throat.[448]
- 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.[449]
- In the later stages of the pandemic, the sensitivity of fever and cough in predicting infection decreased, and the sensitivity of other symptoms (e.g., sore throat, sputum production, headache, myalgia, fatigue, dyspnea, diarrhea) increased.[450]

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.[451]
- 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.[218] [219]
- 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.

Atypical presentations have been reported.

- Atypical presentations may occur, especially in older patients and patients who are immunocompromised (e.g., fatigue, reduced alertness, diarrhea, loss of appetite, delirium, reduced mobility, absence of fever).[444]

- There have been case reports of parotitis (possibly related to intraparotid lymphadenitis), oral vesiculobullous lesions, persistent hiccups, and androgenetic alopecia in patients with COVID-19; however, it is unknown whether there is a causal association.[452] [453] [454] [455]

Coinfections are possible.

- Coinfections can be:
  - Coinfections at presentation
  - Reactivation of latent infections
  - Nosocomial infections
  - Opportunistic fungal infections
- The pooled prevalence of coinfection in SARS-CoV-2-positive patients was 19%, with viral coinfections being more common than bacterial and fungal coinfections.[456]
  - 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. Coinfection with influenza may increase the risk for intensive care unit admission and mechanical ventilation, but does not increase the risk of mortality.[457]
  - The most frequently identified fungi was *Aspergillus* .
- Coinfection with tuberculosis, HIV, and malaria have been reported.[458][459] [460]

Clinical presentation in children and adolescents

Signs and symptoms may be similar to other common viral infections and other childhood illnesses (e.g., influenza, respiratory syncytial virus infection, gastroenteritis), so a high index of suspicion for COVID-19 is required in children and adolescents.[461]

- Children and adolescents usually have fewer and milder symptoms, and they are less likely to progress to severe disease compared with adults.[20] [462] Children and adolescents are also more likely to be asymptomatic.[463] The reasons for this are still under investigation, but children appear to develop a higher and more sustained antibody response compared with adults.[464]
- The frequency of severe disease in children was lower with infection with the Omicron variant compared with Delta and Alpha variants.[465]
- 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.[20]
- The most common symptoms in neonates include fever, inability to feed, lethargy, irritability, feeding difficulties, dyspnea, silent hypoxia, and neurologic symptoms. Cases of late-onset neonatal sepsis and encephalitis have been reported rarely.[437] [466] [467] [468]

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

- Consider 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.[469] For more information, see Complications .

Coinfections are possible in children.

- Coinfections have been documented in 9% of children, with the most common pathogens being respiratory syncytial virus and *Mycoplasma pneumoniae* . Coinfections are less common in children compared with adults.[470]
- Viral coinfection has been associated with a higher frequency of severe outcomes in children, particularly in infants.[465] A higher percentage of children with influenza and SARS-CoV-2 coinfection required noninvasive or invasive respiratory support compared with those with influenza only.[471]

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.[472]
- 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.[473]

Pulse oximetry

Pulse oximetry may reveal low oxygen saturation.

- Hypoxia (hypoxemia) is defined as oxygen saturation <94%, or <88% in the presence of chronic lung disease.[474] However, the oxygen saturation cut-offs used to define disease severity in patients with COVID-19 vary and you should consult your local guidelines.
  - The World Health Organization (WHO) defines severe disease as SpO_2 <90%.[444]
  - In the UK, the National Institute for Health and Care Excellence (NICE) recommends using current NHS guidelines.[405] A reading of <92% is one defining feature of severe disease that requires urgent hospital admission, while a reading of 93% to 94% may indicate moderate disease.[475]
  - In the US, the Infectious Diseases Society of America (IDSA) defines severe disease as SpO_2 <94%.[401]
- 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.[476]

Pulse oximeters may exhibit suboptimal accuracy in certain populations, especially in those who have darker skin. Always interpret SpO_2 within the context of a patient's clinical presentation.

- A systematic review and meta-analysis found that pulse oximetry probably overestimates oxygen saturation compared with SaO_2 (arterial oxygen saturation) in people with high levels of skin pigmentation and people who report their ethnicity as black/African-American (moderate- and low-certainty evidence). The bias of measurements for people with other levels of skin pigmentation or those from other ethnic groups is either more uncertain or suggests no overestimation.[477]
- The 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.[478]

Pulse oximeters can be used at home to detect hypoxia in patients with mild to moderate disease.

- Evidence suggests that patients who may benefit most from monitoring are those who are symptomatic and are either over age 65 years, or are under age 65 years and are extremely clinically vulnerable to COVID-19.[475]
- Home pulse oximetry requires clinical support (e.g., regular phone contact from a health professional).
- [BMJ practice pointer: remote management of covid-19 using home pulse oximetry and virtual ward support] (https://www.bmj.com/content/372/bmj.n677)

Monitoring to identify clinical deterioration

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

- While National Early Warning Score 2 (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 vital signs monitoring to at least hourly until a clinical review happens.[479]
- 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., NEWS2 scores) may not help predict those patients who go on to develop respiratory failure.[476]
- 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.[480]
- A NEWS2 score ≥4 was found to be the best cut-off point for predicting respiratory failure.[481] However, you should consult your local guidance.
- For more information on medical early warning and prognostic scores, see Monitoring .

Initial laboratory investigations

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

- ABG
- CBC
- Comprehensive metabolic panel
- Blood glucose level
- Coagulation screen
- Inflammatory markers (e.g., serum C-reactive protein [CRP], erythrocyte sedimentation rate, lactate dehydrogenase, procalcitonin, and ferritin)
- Cardiac biomarkers

The most common laboratory abnormalities are:[482] [483] [484]

- Lymphopenia
- Leukocytosis
- Leukopenia

- Thrombocytopenia
- Hypoalbuminemia
- Elevated cardiac biomarkers
- Elevated inflammatory markers
- Elevated D-dimer
- Abnormal liver and renal function

For more detailed information on tests and test results, see Tests .

Laboratory abnormalities – in particular, lymphopenia, leukocyte abnormalities, and other markers of systemic inflammation – are less common in children.[485] [486] 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.[487]

A Cochrane review found that while routine laboratory tests used to assess blood clotting and inflammation (i.e., CRP, lactate dehydrogenase, D-dimer, lymphocyte count, neutrophil to lymphocyte ratio) may be used for initial risk stratification (along with clinical signs and symptoms) to assess a patient, none of these tests performed well enough to safely rule out progression to severe or critical disease.[488]

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. Specimens should be collected prior to starting empiric antimicrobials if possible.[444]
- Patients may develop bacterial or fungal coinfections; therefore, it is important to ensure appropriate microbiologic specimens are taken and imaging is ordered, according to local guidelines, when coinfections are suspected.

Overview of SARS-CoV-2 diagnostic testing

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

- Molecular testing
- Rapid antigen testing
- Serologic testing

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.[489]

- Molecular tests: 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: detect viral protein and 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 rapid antigen tests are both negative, or may be useful surveillance tools to inform public policy.

A combination of tests may be required depending on individual patient circumstances (e.g., a symptomatic person with a negative rapid antigen test may require confirmation testing with a molecular test).

The diagnostic accuracy of molecular tests and rapid antigen tests does not appear to be influenced by the Omicron variant.[490]

- A prospective cohort study found that the performance of rapid antigen tests in people infected with the Omicron variant is not inferior to that in people infected with the Delta variant.[491]

Testing strategies vary widely between countries, and you should consult your local public health authority for advice when deciding which test to use.

The WHO recommends the following principles as part of testing programs:[492]

- Test early in the course of COVID-19 to enable timely care and treatment.
- Test to reduce spread.
- Test to track the evolution of the epidemic and the SARS-CoV-2 virus.

Who to test

Widespread screening of asymptomatic people is no longer recommended in most countries. For more information, see Screening .

The WHO recommends testing all people who meet the suspected case definition, regardless of vaccination status or disease history.[493]

- When resources are constrained, suspected cases who are at risk of developing severe disease, those who require hospitalization, 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 people with a risk of exposure including contacts of confirmed or probable cases and frequently exposed occupational groups such as healthcare workers and long-term care facility workers.

In the UK, from 1 April 2024, testing is recommended for the following situations in NHS settings:[494]

- Symptomatic adults and children admitted for care or developing symptoms within hospitals where having COVID-19 will change clinical management: for example, to inform treatment (PCR and lateral flow device at local discretion)
- Symptomatic adults and children eligible for antiviral treatment or in community settings to inform treatment (lateral flow device)
- Discharge of asymptomatic patients to care settings such as care homes or hospices (not routinely required; however, lateral flow devices could be introduced at local discretion based on risk)
- Symptomatic NHS staff and staff in NHS-commissioned independent healthcare providers working on wards focused on treating severely immunosuppressed individuals (lateral flow device in line with locally-derived protocols)
- Outbreak testing in healthcare settings (lateral flow device or PCR in line with locally-directed protocols; PCR where needed for diagnosis)

Testing recommendations for care services (adult social care and hospices) and other nonhealthcare settings are also available.

In the US, testing may be considered in any person with signs or symptoms consistent with COVID-19.[442]

- [CDC: overview of testing for SARS-CoV-2] (https://www.cdc.gov/covid/hcp/clinical-care/overview-testing-sars-cov-2.html)

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The choice of test depends on the clinical scenario. Consult your local public health authority for guidance as testing priorities depend on local recommendations and available resources, and guidance may update regularly.

Molecular testing

Molecular testing is recommended to confirm the diagnosis.

- Order a nucleic acid amplification test, such as RT-PCR, for SARS-CoV-2 in patients with suspected infection, whenever possible.[439]
- 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.[495]

Specimens

- Collect specimens under appropriate infection prevention and control procedures.
- The optimal specimen for testing depends on the clinical presentation and the time since symptom onset. The WHO recommends the following.[439]
  - 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).
  - Saliva specimens: not currently recommended 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 specimens:[496]
  - Upper respiratory specimens: nasopharyngeal or oropharyngeal swab; nasal mid-turbinate swab; anterior nares swab; or nasopharyngeal/nasal wash/aspirate.
  - Lower respiratory specimens: sputum, bronchoalveolar lavage, tracheal aspirate, pleural fluid, or lung biopsy.
- 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.[497] [498]
    - 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.[499] [500] The majority of cases (59%) had no reported predisposing factor in their history. Surgical repair is the recommended treatment option.[501]

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).[439] The pooled sensitivity has been estimated to be 87.8%, with the specificity estimated to be in the range of 87.7% to 100%.[502]
- 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.[439] It is also useful in the context of circulating SARS-CoV-2 variants to differentiate between variants.
- See the Testing limitations and evidence section (below).

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 tuberculosis as appropriate.[444] 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.

Rapid antigen testing

Antigen testing relies on direct detection of SARS-CoV-2 viral proteins in upper respiratory specimens or saliva using a lateral flow immunoassay.[440]

- 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.
- Results are usually available in less than 30 minutes.
- Rapid, lateral flow antigen tests for home use are available over-the-counter in some countries. Laboratory-based (nonrapid) antigen tests may also be available in some countries.

International guidelines for 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.[440] [503]
    - 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.
    - Self-testing should be offered in addition to professionally administered testing services. It should always be voluntary and never mandatory or coercive.
- In the US, the CDC recommends that antigen tests may be used for certain testing situations; however, confirmatory molecular testing may be needed.[442]

See the Testing limitations and evidence section (below).

Serologic testing

Serology cannot be used as a standalone diagnostic test for acute SARS-CoV-2 infections, and should not be used to establish the presence or absence of acute infection.

- However, it may be useful in various settings (e.g, negative molecular testing, diagnosing patients with late presentation or prolonged symptoms, serosurveillance studies).[439] [504]
- 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.[505] [506]
- Results are usually available in up to 24 hours.

International guidelines for the use of serologic tests vary. Consult your local guidance.

- 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.[439]

    - 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.
- IDSA recommends against using serologic testing to diagnose infection during the first 2 weeks following symptom onset or to provide evidence of infection in symptomatic patients with a high clinical suspicion and repeatedly negative molecular tests. Serologic testing may be used to assist with the diagnosis of multisystem inflammatory syndrome in children or when evidence of previous infection is desired.[507]
- [BMJ practice pointer: testing for SARS-CoV-2 antibodies] (https://www.bmj.com/content/370/bmj.m3325)

Rapid antibody detection tests

- 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.[508]
- Evidence is particularly weak for point-of-care serologic tests, and available evidence does not support their use.

    - A meta-analysis found that the overall sensitivity of chemiluminescent immunoassays (CLIAs) for IgG or IgM was approximately 98%, and the sensitivity of enzyme-linked immunosorbent assays (ELISAs) was 84%; however, lateral flow immunoassays (LFIAs), 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.[509]

Testing limitations and evidence

Molecular testing (e.g., RT-PCR) 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.[510]

Interpret RT-PCR test results with caution.

- The evidence for the use of RT-PCR in the diagnosis of COVID-19 is limited, 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.[502]
- 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 recommended test against which any diagnostic index test for viruses must be measured and calibrated, to understand the predictive properties of that test.[511] 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.[512]
- Results can fluctuate from positive to negative at all stages of infection, can become positive again after two consecutive negative tests, can be detected for longer in those with severe infection, and may fluctuate at the level of detection for several weeks. Results may also vary according to the sample site.[58]

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

- RT-PCR may overestimate the duration of infectiousness.[58] 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.[512] 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.[511]
- 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.[513] Another study found that patients with a cycle threshold of 34 or above do not excrete infectious virus.[514] 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.[512]
- Cycle threshold values do not provide a reliable or consistent proxy for infectiousness across SARS-CoV-2 variants.[515]

Interpreting RT-PCR 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.[516]

- 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%.[502]
- 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.[516] When the pretest probability is low, positive results should be interpreted with caution, and ideally a second specimen tested for confirmation.[517]
- Post-test probability: the lower the prevalence of disease in a given population, the lower the post-test probability.[518] For example, if a test with a specificity of 99% is used to test a high-risk symptomatic 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.[519]
- [BMJ practice pointer: interpreting a covid-19 test result] (https://www.bmj.com/content/369/bmj.m1808)

False-positive RT-PCR 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).[520] False-positive results are more likely when the prevalence of SARS-COV-2 is moderate to low.[521]
- There is 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%.[522] 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.[517]
- Examples of the potential consequences of false-positive test results include:[517]
    - Unnecessarily postponing or canceling elective procedures or treatments
    - 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 RT-PCR results

- The FDA 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.[523]

- False-negative rates of between 2% and 29% have been reported.[516] 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.[524]
- 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.[525]
- Examples of the potential consequences of false-negative test results include:[516]
  - Patients may be moved into non-COVID-19 floors leading to spread of hospital-acquired infection.
  - Caregivers could spread infection to vulnerable dependents.
  - Healthcare workers risk spreading the infection to multiple vulnerable individuals.

Evidence for the diagnostic performance of different RT-PCR specimen types is limited.

- 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.[526] Anterior nasal swabs appear to be less sensitive (82% to 88%) compared with nasopharyngeal swabs (98%). Mid-turbinate and anterior nares swabs perform similarly.[527] There was a high concordance between test results from self-swabbing and assisted swabbing.[528]
- 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.[529] [530] [531] [532] [533] [534]
- A Cochrane review found that self-collected samples from the nose, oropharynx, oral cavity, and saliva were less sensitive for detecting COVID-19 compared with healthcare worker-collected nasopharyngeal samples. However, self-collected gargle and deep throat saliva samples had similar sensitivity compared with healthcare worker-collected nasopharyngeal samples.[535]

Rapid antigen tests are more reliable in people with a high viral load who are symptomatic.

- 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.[536] [537]
  - A Cochrane review found that rapid antigen tests vary in sensitivity. Sensitivity was higher in the first week after symptom onset in symptomatic people (80.9%) compared with the second week of symptoms (53.8%). Sensitivity was higher in symptomatic people (73%) compared with asymptomatic people (54.7%). Sensitivity also varied between brands of tests.[538]

    - 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.[539]
    - A systematic review and meta-analysis found that fully self-performed rapid antigen tests, including self-collection of nasopharyngeal or oropharyngeal samples, showed moderate sensitivity and high specificity compared with standard RT-PCR tests. The sensitivity was higher in symptomatic patients when samples were collected within 7 days of symptom onset.[540]
    - A Cochrane review found that self-collected samples from the nose have a similar sensitivity to healthcare worker-collected nasopharyngeal samples.[535]
- Results should be interpreted with caution as false-positive and false-negative results are possible.
    - The FDA has warned that false-positive results can occur with rapid 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.[541]
    - The FDA recommends repeat (or serial) testing following a negative result from an at-home test, regardless of whether symptoms are present, in order to reduce the risk of a false-negative result.[542]
    - Certain tests may not be recommended due to performance issues.

Serologic testing should be used with caution and not be used to determine acute infections.[439]

- A reliable diagnosis is often only possible in the recovery phase when opportunities for management or interruption of transmission have passed.[439]
- The presence of antibodies that bind to SARS-CoV-2 does not guarantee that they are neutralizing antibodies, or that they offer protective immunity.[439]
- Evidence for the use of serologic testing is limited and uncertainties about its accuracy remain.
    - A Cochrane review found that antibody tests could be a useful tool for patients in whom molecular- or antigen-based tests have failed to detect SARS-CoV-2 virus, including in those with ongoing symptoms of acute infection (from week 3 onwards) or those presenting with post-acute sequelae. Test sensitivity is too low during the first week since the onset of symptoms.[543]
    - 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%. More evidence is needed about the efficacy of testing outside of hospital settings and in asymptomatic or mild cases.[502]

Chest imaging

Imaging should be used as one element of the diagnostic workup that otherwise includes clinical and laboratory data.[544]

- Choice of imaging modality depends on various factors and you should consult your local protocols.
- All imaging procedures should be performed according to local infection prevention and control procedures.

- Chest imaging is considered safe in pregnant women.[545]

Order a chest x-ray in all patients who are seriously ill (e.g., SpO_2 <94% or NEWS2 score ≥3) or those who are stable but a chest x-ray is clinically indicated (e.g., suspected pneumonia).[443]

- 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.[546]
- 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 73% of people who had the disease. However, it incorrectly identified COVID-19 in 27% of people who did not have the disease.[547]
- 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.[544]

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.[548] 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.[443] [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.[549]
  - 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.[550]
- Chest CT is moderately sensitive (70%) and highly specific (90%) for the diagnosis of COVID-19.[551]
  - Pooled results found that chest CT correctly diagnosed COVID-19 in 87% of people who had the disease. However, it incorrectly identified COVID-19 in 21% 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.[547]
  - 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.[552] [553]

DIAGNOSIS

- Accuracy appears to be lower among children; however, there are limited data in this population.[548]

- Chest CT results may not correlate with RT-PCR test results or clinical presentation.
    - Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[554]
    - Some patients may present with a normal chest finding despite a positive RT-PCR.[555]
    - 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.[556]
    - 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).[557]
    - Patients with Omicron variants of SARS-CoV-2 were less likely to be CT-positive compared with those infected with non-Omicron variants.[558]

Typical features of chest CT include ground-glass opacity and consolidation.

- Abnormal chest CT findings have been reported in up to 97% of hospitalized patients.[559]
    - 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.[560]
    - Atypical features include pulmonary vascular enlargement, adjacent pleural thickening, air bronchograms, subpleural lines, bronchus distortion, bronchiectasis, vacuolar retraction sign, and halo sign. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have been reported rarely.[560]
- Ground-glass opacity has the highest diagnostic performance for COVID-19 pneumonia, followed by ground-glass opacity plus consolidation, and consolidation only.[561]
    - 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%).[562]
    - 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.[560]
    - 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.[563]
- Patients with non-Omicron variants of SARS-CoV-2 had more imaging changes on CT compared with those with Omicron variants.[558]
    - Patients with Omicron variants typically had lesions located in the center of the lung or in a single lobe. They were less likely to have bilateral lesions, crazy-paving pattern, linear opacity, and vascular enlargement, but were more likely to have bronchial wall thickening. The distribution of lesions was more extensive (bilateral and multilobe involvement) in patients with non-Omicron variants.

- Pregnant women appear to present more commonly with more advanced CT findings compared with the general adult population.[564]
    - However, CT results are similar to those in the general adult population.
- 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.[565]
    - Ground-glass opacity and peribronchial thickening were the most prevalent findings in infants younger than 1 year of age.[566]

Lung ultrasound may be an alternative to chest x-ray and chest CT in some locations.

- 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.[544]
    - [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas] (https://www.bsti.org.uk/media/resources/files/Lung_US_print_out_and_scoring_proforma.pdf)
- Lung ultrasound is sensitive but not specific for the diagnosis of COVID-19.
    - Pooled results found that lung ultrasound correctly diagnosed COVID-19 in 87% of people with the disease. However, it incorrectly diagnosed COVID-19 in 24% 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.[547]
    - Lung ultrasound score was a good predictor of poor outcome and 28-day mortality in one study.[567]
- Typical features include B-lines (confluent or separated and usually at least 3) and pleural abnormalities, with a bilateral distribution.[568]
    - Other findings include consolidations, pleural effusion, air bronchogram, and pneumothorax.
    - While these findings are not specific for COVID-19, they may increase the likelihood of disease in the context of a characteristic clinical presentation.
- Lung ultrasound has advantages and limitations.[569] [570] [571]
    - Advantages: portability; bedside evaluation; reduced healthcare worker exposure; easier sterilization process; absence of ionizing radiation exposure; repeatability during follow-up; safe to use in pregnant women and children; more readily available in resource-limited settings.
    - Limitations: unable to discern chronicity of a lesion; other imaging modalities may be required.
- 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).[572] Lung ultrasound score may play a role in prognosis.[573]

The WHO recommends chest imaging (chest x-ray, chest CT, or lung ultrasound) in the following scenarios:[544]

- 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 floor 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)

History and exam

Key diagnostic factors

fever (common)

- Reported in approximately 64.6% of patients.[436] The course may be prolonged and intermittent, and some patients may have chills/rigors. In children, fever may be absent or brief and rapidly resolving.[574] [575] Data from the UK COVID Symptom Study report that fever is much less common now compared with early SARS-CoV-2 variants.[576]

cough (common)

- Reported in approximately 53.6% of patients.[436] The cough is usually dry; however, a productive cough has been reported in some patients. Can persist for weeks or months after infection.[577] Data from the UK COVID Symptom Study report that cough (with or without phlegm) is one of the most common symptoms.[576]

dyspnea (common)

- Reported in approximately 19.8% of patients.[436] Associated with increased severity of disease.[578] Wheezing has been reported in 16.9% of patients.[436]

altered sense of smell/taste (common)

- Anosmia has been reported in approximately 18.7% of patients, and ageusia in 17.4% of patients.[436] Pathognomonic for previously circulating SARS-CoV-2 variants, but is less prevalent in people infected with the Omicron variant.[449] [579] [580] May be an early symptom before onset of other symptoms, or may be the only symptom.[581] Most patients recover within 30 days.[582] However, persistent smell or taste dysfunction may develop in approximately 5% of patients.[583] The majority of patients recover within 1 to 2 years.[584] [585] Parosmia (misperception of an odor) has been reported as a late-onset symptom.[586] Many drugs are associated with taste and smell changes (e.g., antibiotics, ACE inhibitors) and should be considered in the differential diagnosis.[587] Data from the UK COVID Symptom Study report that altered sense of smell is one of the most common symptoms.[576]

Other diagnostic factors

fatigue (common)

- Reported in approximately 29.4% of patients.[436] Fatigue and exhaustion may be extreme and protracted, even in patients with mild disease.

myalgia or arthralgia (common)

- Myalgia has been reported in approximately 18.7% of patients, and arthralgia in 7.5% of patients.[436] Arthritis has been reported rarely.[588] Data from the UK COVID Symptom Study report that myalgia is one of the most common symptoms.[576]

sore throat (common)

- Reported in approximately 12.4% of patients.[436] 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.[576]

headache (common)

- Reported in approximately 11% of patients.[436] Data from the UK COVID Symptom Study report that headache is one of the most common symptoms.[576]

rhinorrhea or nasal congestion (common)

- Rhinorrhea has been reported in approximately 7% of patients, and nasal congestion in 5.1% of patients.[436] Data from the UK COVID Symptom Study report that rhinorrhea and nasal congestion are two of the most common symptoms.[576]

sneezing (common)

- Reported in approximately 4.4% of patients.[436] Data from the UK COVID Symptom Study report that sneezing is one of the most common symptoms.[576]

expectoration (common)

- Reported in approximately 23.4% of patients.[436]

chest pain/tightness (common)

- Chest distress has been reported in approximately 12.7% of patients, and chest pain in 5.8% of patients.[436] May indicate pneumonia.

malaise (common)

- Reported in approximately 12.1% of patients.[436]

dizziness (common)

- Reported in approximately 7.2% of patients.[436] May be a direct consequence of the virus affecting vestibular function, or may be an indirect effect of hypoxia, dehydration, or fever.[589]

confusion or delirium (common)

- Confusion has been reported in approximately 6.4% of patients, and delirium in 17.5% of patients.[436] Delirium has been associated with a 3-fold increase in mortality, and there is an increased prevalence in people age >65 years.[590] Risk factors for delirium include benzodiazepine use and the lack of family visitation.[591]

gastrointestinal symptoms (common)

- Generally reported in <20% of patients. Anorexia has been reported in 12.9% of patients, diarrhea in 8.1% of patients, nausea in 6.7% of patients, vomiting in 5.5% of patients, and abdominal pain in 3.7% of patients. Other less common symptoms include constipation, heartburn, hematemesis, melena, and hematochezia.[436] More common in children.[437] Has been associated with increased severity of disease.[592] [593] [594] Patients who shed fecal viral RNA for longer periods of time may report ongoing gastrointestinal symptoms.[595]

cutaneous symptoms (common)

- Generally reported in <20% of patients. Rash has been reported in 14% of patients, chilblain-like lesions in 24.6% of patients, urticaria in 16.8% of patients, chickenpox-like vesicles in 16.2% of patients, and livedo reticularis in 4.6% of patients. Lesions may be erythematous, vesicular, pustular, ulcerative, edematous, petechial, or pruritic.[436] May be the only, or the first, presenting sign in children or adults.[596] [597] [598] Severe and potentially life-threatening mucocutaneous dermatologic manifestations have been reported.[599] Further data are required to better understand cutaneous involvement and whether there is a causal relationship as there is conflicting evidence.[600] [601] [602]

ocular symptoms (common)

- Generally reported in 5% to 20% of patients. Dry eye has been reported in 14.5% of patients, tearing in 12.8% of patients, itching in 9.2% of patients, eye pain in 6.9% of patients, and conjunctivitis in 5.5% of patients. Other less common symptoms include photophobia, chemosis, conjunctival congestion, blurred vision, and lid edema. Relatively rare in children and pregnant women.[436] May be the initial presenting symptom. Usually mild with no complications.[603] However, retinal complications have been reported.[604] [605] [606] Has been associated with increased severity of disease.[607]

signs of pneumonia or acute respiratory distress (uncommon)

- Bronchial breath sounds may indicate pneumonia. Tachypnea, tachycardia, crackles/rales (on auscultation), or cyanosis may be present in patients with acute respiratory distress.

hemoptysis (uncommon)

- Reported in approximately 1.8% of patients.[436] May be a symptom of pulmonary embolism.[608]

audio-vestibular symptoms (uncommon)

- Sudden sensorineural hearing loss (SSNHL), tinnitus, and rotatory vertigo have been reported in 7.6%, 14.8%, and 7.2% of patients, respectively. Otalgia has also been reported.[609] Data on SSNHL in patients with COVID-19 are inconsistent and contradictory. Therefore, it remains unknown whether COVID-19 contributes to the incidence of SSNHL.[610]

oral mucosal lesions (uncommon)

- 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.[611] SARS-CoV-2–associated reactive infectious mucocutaneous eruption has also been reported.[612] 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.[613]

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 (WHO) 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 determined by local health authorities based on 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]

residence/work in location with high risk of transmission

- People who live or work in 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 settings, humanitarian settings) and people working in a health setting (including within health facilities and households) are at higher risk of infection.[124]

older age

- Older people are at increased risk for infection and severe disease.[18]
- 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 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.[125]
- According to US data, the risk of death is 340 times higher in people ages 85 years and older compared with 18- to 29-year-olds.[126]
- 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.[127] The highest mortality rate was observed in patients 80 years and older.[128]
- 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.[129]
- 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.[130]

male sex

- Males are at increased risk for infection and severe disease.[18]
- A meta-analysis found that men have a higher risk for infection, hospitalization, disease severity, intensive care unit admission, and death.[131]

- Various hypotheses have been proposed to explain the difference including androgen-driven pathogenesis (evidence is weak), immunologic protective effect of estrogen in females (conflicting evidence), testosterone deficiency-induced inflammatory storm (limited conflicting evidence), and inborn error of cytokine immunity (requires more investigation). The cause is likely multifactorial with overlapping features of various hypotheses.[132]

ethnicity

- People who belong to racial/ethnic minority populations may be at increased risk of infection, severe disease, hospitalization, intensive care unit admission, and death to varying extents across ethnic groups.[133] [134] [135] [136] 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.[137] [138] [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.[135]
- 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.[126] [145]
- 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.[146] 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.[147]
- 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.[148]

presence of comorbidities

- People with comorbidities are at increased risk for severe disease, and the more comorbidities, the greater the risk.[126] [149]
- 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%).[150] 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.[126] The risk of severe disease increases as body mass index (BMI) increases.[158] Obesity was highly prevalent in patients with COVID-19, with a pooled prevalence of 32% (37% in those requiring intensive care admission).[159]
- 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.[160]
- Evidence from meta-analyses 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. Being overweight increases the risk of hospitalization, but not death.[161] [162] However, the strength of association appears to have weakened over time.[162]
- 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 BMI ≥23 kg/m², independent of the excess risks of related diseases (e.g., diabetes). The relative risk was particularly notable in people age <40 years and those with black ethnicity. Every unit increase in BMI increased the risk of: hospital admission by 5% (above BMI ≥23 kg/m²); intensive care admission by 10% (any BMI); and death by 4% (BMI ≥28 kg/m²).[163]
- A cohort study in the US found a nonlinear relationship between BMI and disease severity, with the lowest risk at BMIs near the threshold between healthy weight and overweight, then increasing with higher BMI.[164]

cardiovascular disease

- People with cardiovascular disease are at increased risk for severe disease.[126]
- Preexisting cardiovascular disease is associated with adverse outcomes including disease severity, disease progression, and mortality in adults and children.[165] [166]

- 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.[167] Preexisting atrial fibrillation/atrial flutter was associated with a higher risk of intensive care admission, in-hospital mortality, and worse outcomes.[168] [169] 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.[170] Myocardial injury and peripheral artery disease are also associated with increased short-term mortality.[171] [172]
- People with risk factors for cardiovascular disease (e.g., hypertension, diabetes) are also at increased risk for severe disease and mortality (see below).[173] [174]

diabetes

- People with type 1 or type 2 diabetes are at increased risk for severe disease.[126]
- 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. 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. Data are mixed on whether type 1 diabetes predisposes a person to a higher risk from infection compared with type 2 diabetes. There are no data to suggest that diabetes increases the risk of severe disease in children and adolescents.[175] [176] Variability across different regions in the world is significant and may skew overall trends.[177]
- 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.[178] [179] [180] [181] [182] [183] [184] Poor glycemic control in critically ill patients increases the risk of complications and mortality.[185] 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.[175]
- Use of metformin, sodium–glucose cotransporter-2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists was associated with lower mortality in patients with type 2 diabetes. Dipeptidyl peptidase-4 (DPP-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.[186] [187] 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.[188] [189]
- Infection is also associated with an elevated risk of new incident diabetes. The risk is associated with hospitalization and receiving intensive care.[190]

chronic respiratory disease

- People with chronic lung diseases such as asthma, 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 bronchopulmonary dysplasia or alpha-1 antitrypsin deficiency may be at increased risk for severe disease; however, evidence is limited.[126] There is no clear evidence that people with asthma or COPD are at higher risk of infection.[191] [192]
- COPD: associated with an increased risk of hospitalization, intensive care unit admission, and mortality.[193] [194] 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.[195]
- 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.[196] [197] Asthma was associated with an increased risk of hospitalization in children; however, use of inhaled corticosteroids was associated with a reduced risk of infection.[198]
- 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.[199] [200]
- 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).[201] Other risk factors for severe outcomes include FEV_1 <70%, age >40 years, diabetes, pancreatic insufficiency, underweight, and use of azithromycin.[202] Post-lung transplantation and cystic fibrosis-related diabetes were risk factors for severe disease in children.[198]
- Active pulmonary tuberculosis: appears to be associated with an increased risk of severe disease and mortality.[203] [204]
- Interstitial lung disease: appears to be associated with an increased risk of severe disease and mortality.[205] [206]

chronic kidney disease

- People with chronic kidney disease (including those receiving dialysis) are at increased risk for severe disease, and may be at higher risk for infection.[126] [127]
- 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.[207]
- Incidence appears to be higher in patients receiving dialysis compared with those not requiring renal replacement therapy.[208] 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.[209]

- 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%).[127]
- Preexisting chronic kidney disease is an independent risk factor for developing acute kidney injury as a complication.[210]

chronic liver disease

- People with chronic liver disease such as cirrhosis, metabolic dysfunction-associated fatty liver disease (nonalcoholic 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.[126]
- Chronic liver disease has been associated with an increased risk for severe disease and mortality, but not an increased risk of infection.[211] Higher liver fibrosis scores are associated with worse prognosis.[212]
- 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.[213] Alcohol consumption is associated with an increased risk of severe disease, hospitalization, and intensive care unit admission.[214]
- People with metabolic dysfunction-associated fatty liver disease are at increased risk for severe disease.[215] Disease severity has been associated with age <60 years and intermediate or high fibrosis-4 (FIB-4) scores.[216] [217]

pregnancy

- Pregnant women are at increased risk for severe disease.[126]
- 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.[218] [219] 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.[220]
- 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.[221]
- Mortality rates vary significantly between geographic regions, with the highest rates in Sub-Saharan Africa and Latin America and the Caribbean, and by country income groups, with the highest rates in low-income countries.[222]
- Risk factors for pregnant women developing severe disease, maternal morbidities, and adverse birth outcomes included age ≥30 years, mixed ethnicity, gestational diabetes, diabetes, hypertension, cardiovascular disease, kidney disease, overweight/obesity, HIV infection, pre-pregnancy underweight, and anemia.[223] [224] [225]
- For more information on pregnancy-related complications, see Complications .

smoking

- People who are current or former smokers are at increased risk for severe disease.[126]
- 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.[226] Current or former smokers (ever smokers) had a 16% higher risk of being hospitalized, a 44% higher risk of more severe disease, a 39% higher

risk of mortality, and 45% higher risk for disease progression, compared with nonsmokers (never smokers).[227] This may be due to increased airway expression of the angiotensin-converting enzyme-2 receptor in smokers.[228] The risk of mortality in current smokers does not appear to vary by age; however, the risk drops significantly by age in former smokers.[229]
- The World Health Organization (WHO) has reviewed the available evidence and concluded that smoking is associated with increased severity of disease and death in hospitalized patients.[230]

malignancy

- People with cancer (including hematologic malignancies) are at increased risk for infection and severe disease.[126] [231]
- Patients with cancer have an increased risk of infection, severe disease, intensive care unit admission, and mortality compared with the general population.[232] 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.[233]
- The pooled in-hospital mortality risk in patients with cancer is 14.1%.[234] The pooled mortality in cancer patients admitted to the intensive care unit is 60.2%.[235] 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.[236]
- 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.[237] Patients receiving immune checkpoint inhibitors do not appear to be at an increased risk of poor clinical outcomes compared with patients not receiving oncologic treatment or other cancer therapies, but evidence is limited.[238]
- 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.[239] 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.[240] 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.[241] Limited evidence suggests that no severe complications were associated with continuation of chemotherapy in children who test positive for SARS-CoV-2.[242]

cerebrovascular disease

- People with cerebrovascular disease are at increased risk for severe disease.[126]
- Patients with a history of cerebrovascular disease were more likely to progress to adverse outcomes compared with patients without a history of cerebrovascular disease.[243] Patients with preexisting cerebrovascular disease had 2.67-fold higher odds of poor outcomes including intensive care admission, mechanical ventilation, and mortality.[244] Previous stroke was significantly associated with severe disease, intensive care unit admission, mechanical ventilation, and mortality.[245]

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.[126]
- People with preexisting mental health disorders have an increased risk of hospitalization and mortality compared with patients without mental health disorders.[246] [247]
- People with preexisting schizophrenia may be at increased risk of mortality. Risk factors include older age and a history of smoking.[248]

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.[126]
- 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.[249]
- 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.[250]

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 (among others) are at increased risk for severe disease.[126]
- In the UK, a cohort study found a 4-fold increased risk for hospitalization and a 10-fold increased risk for for mortality in people with Down syndrome.[251] This may possibly be due to the presence of immune dysfunction, congenital heart disease, and pulmonary pathology. Also, people with Down syndrome often have associated obesity and obstructive sleep apnea, both of which are risk factors for worse outcomes. The mortality rate was higher in those over age 40 years in one systematic review.[252]
- 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.[253]
- 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.[254]

dementia

- People with dementia may be at increased risk for infection and are at increased risk for severe disease.[126] [255]
- 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.[256]

- 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.[257]
- 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.[258]

Parkinson disease

- People with Parkinson disease may be at increased risk for infection and are at increased risk for severe disease.[126] [259] [260] [261]
- Risk factors for infection may include obesity, pulmonary disease, and hospitalization. Vitamin D supplementation was associated with a lower risk of infection.[260]
- 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.[259]
- Patients may experience substantial worsening of parkinsonian symptoms.[262]

immunosuppression

- People who are immunocompromised are at increased risk for severe disease.[126] People with immunocompromising conditions have a higher risk of hospitalization and mortality.[263]
- This includes people with a history of primary immune deficiencies or prolonged use of corticosteroids or other immunosuppressant medications.
- Once hospitalized, immunocompromised people are at increased risk for intensive care unit admission and death, irrespective of vaccination status, compared with nonimmunocompromised patients (after adjusting for differences in clinical and demographic characteristics).[264]
- 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.[265] Glucocorticoid exposure of ≥10 mg/day (prednisone) has been associated with a higher odds of hospitalization in patients with rheumatologic disease.[266] 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.[267]
- Immunosuppressed patients are not at significantly increased risk of infection compared with the general population.[268]
- Also see HIV infection and Autoimmune disease below.

HIV infection

- People living with HIV are at increased risk for severe disease.[126]
- 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.[269] [270] [271] [272] 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.[273]

- Evidence from individual studies, systematic reviews, and meta-analyses is conflicting. Some have found that HIV infection was not associated with composite poor outcome or mortality, while others have found that people living with HIV infection have an increased risk for infection and mortality compared with people without HIV.[274]
- The World Health Organization (WHO) 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.[275] [276] Other risk factors for severe illness include coexisting cardiovascular disease, respiratory disease, and chronic kidney disease.[277]

physical inactivity

- People who are not physically active are at increased risk for severe disease.[126]
- Data indicate an association between physical inactivity and an increased risk of hospitalization and mortality, and possibly an association between physical inactivity and increased risk of ventilation. There are limited data on the association between physical inactivity and intensive care unit admission and intubation.[278] [279] [280] Moderate-to-vigorous physical activity reduced the odds of infection, hospitalization, and mortality compared with no physical activity.[281]

hemoglobin disorders

- People with sickle cell disease or thalassemia may be at increased risk for severe disease; however, evidence is limited.[126] People with sickle cell disease or trait are at increased risk of hospitalization and mortality.[282]
- 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.[283] [284]
- 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.[285]
- 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.[286] Infection can cause acute chest syndrome in patients with sickle cell disease.[287] [288]

hemophilia

- People with hemophilia may be at increased risk for severe disease; however, evidence is limited.[126]
- People with hemophilia were more likely to have moderate disease and be admitted to hospital compared with those without hemophilia in one retrospective study. Hemophilia increased the risk of bleeding in patients with COVID-19, and was not protective against venous thromboembolism despite the hypocoagulable state. There was no significant difference between mortality rates, or other markers of disease severity (e.g., intensive care unit admission, need for oxygen).[289]

hypertension

- People with hypertension may be at increased risk for severe disease; however, evidence is limited.[126]
- 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.[290] [291]
- 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.[292] [293] 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.[294] [295]
- 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.[296] 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.[297] [298]

epilepsy

- People with epilepsy may be at increased risk for severe disease; however, evidence is limited.[126]
- Older adults (age ≥65 years) with epilepsy had a significantly higher risk of inhospital mortality and longer length of hospital stay compared with those without epilepsy in one retrospective study.[299]

substance use disorders

- People with substance use disorders may be at increased risk for severe disease; however, evidence is limited.[126] 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.[300] [301] A systematic review and meta-analysis found that people with opioid use disorder have an increased risk of hospitalization, intensive care unit admission, and mortality.[302]

children with certain underlying conditions

- Children with certain underlying conditions may be at increased risk for severe disease; however, evidence is limited.[126] The presence of at least one comorbidity was associated with a markedly increased risk for critical disease in children.[303]
- 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.[126]
- 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.[304]

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.[305] [306] [307] [308] [309] [310] [311] However, it is unclear whether these associations were statistically significant and the certainty of evidence is very low.[312] [313] When the analyses included studies with adjustments for confounders, vitamin D deficiency was not associated with an increased risk of mortality.[314]
- 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.[315]

proton-pump inhibitor use

- People taking proton-pump inhibitors (PPIs) may be at increased risk for infection and severe disease; however, evidence is limited.[316]
- 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.[316]
- 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.[317]

corticosteroid use

- While corticosteroids are used for the treatment of COVID-19 to reduce mortality, long-term use of oral corticosteroids for another condition prior to the development of COVID-19 was found to increase hospitalization, intensive care unit admission, and mortality compared with nonusers, according to one population-based cohort study.[318]

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.[319] [320]
- 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.[265] Tumor necrosis factor (TNF)-alpha inhibitor monotherapy was associated with a lower risk of hospitalization or death among patients with immune-mediated inflammatory disorders compared with other treatment regimens (e.g., methotrexate, azathioprine, Janus kinase [JAK] inhibitors).[321] 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.[322]

inflammatory arthritis

- People with inflammatory arthritis may be at higher risk for infection and severe disease; however, evidence is limited.
- 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.[265]

inflammatory bowel disease

- People with inflammatory bowel disease may be at higher risk for infection and severe disease; however, evidence is limited.
- Prevalence in patients with inflammatory bowel disease appears to be low.[323] [324] Inflammatory bowel disease was not associated with an increased risk of hospitalization, intensive care unit admission, or mortality.[325] 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.[265] Corticosteroid use was associated with an increased risk for severe disease and intensive care unit admission, but not mortality.[326] Higher disease activity and flares may lead to increased susceptibility to infection and worse outcomes.[327]
- Patient outcomes (hospitalization, intensive care unit admission, and mortality) were worse in ulcerative colitis (compared with Crohn disease), and patients on corticosteroids, thiopurines, aminosalicylates, or combination therapy. Outcomes were better in patients on biologic agents.[323] [325] [328] [329] [330]
- A risk calculator has been developed that predicts which patients with inflammatory bowel disease are at higher risk of adverse outcomes.[331]

connective tissue disease

- People with connective tissue disease may be at higher risk for infection and severe disease; however, evidence is limited.
- 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 is a lack of data regarding outcomes and evidence is conflicting.[265]
- Patients with lupus nephritis were at increased risk of developing severe or critical disease.[332]

vasculitis

- People with vasculitis may be at higher risk for infection and severe disease; however, evidence is limited.
- 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.[333] [334]

multiple sclerosis

- People with multiple sclerosis may be at higher risk for infection and severe disease; however, evidence is limited.
- Neurologic disability, older age, black race, cardiovascular comorbidities, recent treatment with corticosteroids, and obesity were risk factors for severe disease and mortality.[335] [336] The risk of

severe disease was higher in patients with progressive disease compared with those with relapsing-remitting disease. Use of anti-CD20 therapies was associated with an increased risk of severe disease in patients with relapsing-remitting disease.[337]
- 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).[338]
- Current evidence does not suggest that patients with multiple sclerosis who are infected with SARS-CoV-2 are at an increased risk of relapse.[339]

thyroid disease

- People with hypothyroidism may be at higher risk of severe disease; however, evidence is limited.[340] [341]
- 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.[342] [343]

gout

- Gout appears to be associated with an increased risk for infection and mortality; however, evidence is limited.[344]
- 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.[344] 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.[345] [346] [347]
- The association was stronger in males, older age, and those with hypertension.[348]
- 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.[296] However, so far, studies do not support this hypothesis, and studies have shown a protective effect (lower risk of mortality or severe disease).[349] 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.[350] Similar findings have been reported from a Swedish registry study.[351]

surgery

- Surgical mortality and complications may be higher in patients with COVID-19 compared with patients without COVID-19.[352]
- 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.[353]

- 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.[354]

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.[355] [356] [357] [358]
- 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.[355] [359] [360]
- 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.[361] 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.[362]

gut dysbiosis

- There is limited evidence that gut and lung microbiota dysfunction may be implicated in the pathogenesis of COVID-19.[363]
- A dysbiotic gut bacterial profile has been noted during the acute and recovery phases.[364] 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.[365] [366] [367] 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.[368]

zinc deficiency

- People with zinc deficiency may have a higher risk of mortality; however, evidence is limited and the exact role of zinc in COVID-19 is not well understood.
- One meta-analysis found that patients with zinc deficiency had a higher risk of mortality and symptomatology compared with those without zinc deficiency. No association was found between zinc levels and the severity of symptoms. However, further research is required.[369]

Tests

1st test to order

Test	Result
real-time reverse transcription polymerase chain reaction (RT-PCR) • Order an RT-PCR for SARS-CoV-2 in patients with suspected infection, whenever possible.[439] Commonly used assays are expected to be able to detect SARS-CoV-2 variants.[495] Genomic sequencing may be performed to differentiate between variants. • Testing strategies vary widely between countries and you should consult your local guidance. For more detailed information on who to test and choice of test see Diagnostic approach . • The optimal specimen for testing depends on the clinical presentation and the time since symptom onset. The World Health Organization (WHO) 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.[439] [496] [614] • 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).[439] The pooled sensitivity has been estimated to be 87.8%, with the specificity estimated to be in the range of 87.7% to 100%.[502] • Molecular testing is an aid to diagnosis only and results should be interpreted with caution. For detailed information on testing limitations and evidence, see Diagnostic approach . • 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, including over-the-counter at-home tests. • Collect nasopharyngeal swabs to rule out influenza and other respiratory infections according to local guidance.[444] 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.	**positive for SARS-CoV-2 viral RNA; may be positive for influenza A and B viruses and other respiratory pathogens**
rapid antigen test • Rapid antigen tests may be used in some settings as an alternative to (or in addition to) RT-PCR. Testing strategies vary widely between countries and you should consult your local guidance.[440] [442][503] [615] For more detailed information on who to test and choice of test, see Diagnostic approach . • While antigen tests are substantially less sensitive than RT-PCR, particularly in asymptomatic people, they offer the possibility of rapid,	**positive for SARS-CoV-2 virus antigen**

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Test	Result
• inexpensive, and early detection of the most infectious cases in appropriate settings.[440] Results are usually available in less than 30 minutes. • A Cochrane review found that rapid antigen tests vary in sensitivity. Sensitivity was higher in the first week after symptom onset in symptomatic people (80.9%), compared with the second week of symptoms (53.8%). Sensitivity was higher in symptomatic people (73%), compared with asymptomatic people (54.7%). Sensitivity also varied between brands of tests.[538] • Rapid antigen tests are an aid to diagnosis only and results should be interpreted with caution. For detailed information on testing limitations and evidence, see Diagnostic approach . • Rapid, lateral flow antigen tests for home use are available in some countries. Laboratory-based (nonrapid) antigen tests are also available in some countries. • [BMJ: interpreting a lateral flow SARS-CoV-2 antigen test] (https://www.bmj.com/content/373/bmj.n1411)	
pulse oximetry • Pulse oximetry may reveal hypoxia/hypoxemia (i.e., oxygen saturation <94%, or <88% in the presence of chronic lung disease).[474] • The World Health Organization (WHO) defines severe disease as SpO_2 <90%.[444] In the UK, a reading of <92% is one defining feature of severe disease that requires urgent hospital admission, while a reading of 93% to 94% may indicate moderate disease.[475] In the US, the Infectious Diseases Society of America (IDSA) defines severe disease as SpO_2 <94%.[401] • 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.[476] • Pulse oximeters may exhibit suboptimal accuracy in certain populations, especially in those who have darker skin.[477] The 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.[478] • Pulse oximeters can be used at home to detect hypoxia in patients with mild to moderate disease. Evidence suggests that patients who may benefit most from monitoring are those who are symptomatic and are either over age 65 years, or are under age 65 years and are extremely clinically vulnerable to COVID-19.[475] Home pulse oximetry requires clinical support (e.g., regular phone contact from a health professional). • [NHS England: 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) • [BMJ practice pointer: remote management of covid-19 using home pulse oximetry and virtual ward support] (https://www.bmj.com/content/372/bmj.n677)	**may show low oxygen saturation (cut-off depends on local guidelines)**

Test	Result
ABG • Order in patients with severe illness as indicated to detect hypercarbia or acidosis. • Recommended in patients with respiratory distress and cyanosis who have low oxygen saturation.	**may show low partial oxygen pressure**
CBC • Order in patients with severe illness. • 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.[616] • Anemia is common and may be associated with a higher risk of mortality.[617] • 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.[618] • Absolute counts of major lymphocyte subsets, particularly CD4+ and CD8+ T-cell counts, are significantly decreased in patients with severe disease.[619] • Late-phase thrombocytopenia (i.e., occurring 3 weeks or more after symptom onset) has been reported but is uncommon.[620]	**lymphopenia; leukocytosis; leukopenia; thrombocytopenia; decreased eosinophils; decreased hemoglobin**
comprehensive metabolic panel • Order in patients with severe illness. • 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.[616] • Hypokalemia has been reported in 54% of patients.[621] Hypocalcemia has been reported and is associated with poor outcomes.[622] Hyponatremia has been reported in 24% of patients, and is associated with poor outcomes.[623] Other electrolyte derangements may be present.	**elevated liver enzymes; elevated total bilirubin; renal impairment; hypoalbuminemia; electrolyte derangements**
blood glucose level • Order in patients with severe illness. • Fasting hyperglycemia independently predicts poor prognosis and is associated with an increased risk of mortality, regardless of whether or not the patient has diabetes.[624] [625] • Hypoglycemia has also been associated with increased mortality in a retrospective cohort study.[626] • Infection is associated with an increased risk of new-onset diabetes. Therefore, monitoring for hyperglycemia during admission should be considered.[627]	**variable**
coagulation screen • Order in patients with severe illness. • 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.[616] [628] • The risk of severe disease and mortality is 2-fold and 4-fold higher, respectively, in patients with elevated D-dimer levels.[629]	**elevated D-dimer; prolonged prothrombin time; elevated fibrinogen; prolonged INR**

Test	Result
Patients with very high D-dimer levels have an increased risk of thrombosis.[630] [631] • Prolonged international normalized ratio (INR) values have been associated with more severe disease and mortality.[632] • Von Willebrand factor markers may be increased, especially in patients with critical disease, and may have prognostic value.[633]	
cardiac biomarkers • 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.[634] • CK-MB has been found to be elevated in mild disease in children. The significance of this is unknown.[486]	**may be elevated**
serum C-reactive protein • Order in patients with severe illness. • Elevated C-reactive protein is significantly associated with severe disease, and may be useful for predicting disease progression.[616] [635] • 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.[636]	**may be elevated**
serum erythrocyte sedimentation rate • Order in patients with severe illness. • Commonly elevated in patients with COVID-19.[484]	**may be elevated**
serum lactate dehydrogenase • Order in patients with severe illness. • Elevated serum lactate dehydrogenase is significantly associated with severe disease, and may be useful for predicting disease progression.[616]	**may be elevated**
serum procalcitonin • Order in patients with severe illness. • Elevated serum procalcitonin is significantly associated with severe disease, and may be useful for predicting disease progression and mortality.[616] [637] • Elevated serum procalcitonin may be more common in children.[638] • May be elevated in patients with secondary bacterial infection.[29] [30] • 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.[405] Do not perform procalcitonin testing without an established, evidence-based protocol.[639]	**may be elevated**
serum ferritin level • Order in patients with severe illness. • Elevated ferritin is significantly associated with severe disease, and may be useful for predicting disease progression.[640] • May indicate development of cytokine release syndrome.[641]	**may be elevated**

Test	Result
blood and sputum cultures • 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.[444] • Specimens should be collected prior to starting empiric antimicrobials if possible.[444]	**negative for bacterial infection**
chest x-ray • Order in all patients who are seriously ill (e.g., SpO_2 <94% or National Early Warning Score 2 [NEWS2] score ≥3) or those who are stable but a chest x-ray is clinically indicated (e.g., suspected pneumonia).[443] • 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.[546] • 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 73% of people who had the disease. However, it incorrectly identified COVID-19 in 27% of people who did not have the disease.[547] • 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.[544]	**ground-glass opacity; consolidation**

Other tests to consider

Test	Result
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.[549] • 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.[550] • Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[554] Some patients may present with a normal chest finding despite a positive RT-PCR.[555] 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.[556] 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).[557] • Abnormal chest CT findings have been reported in up to 97% of hospitalized patients.[559] 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. Atypical features include pulmonary vascular enlargement, adjacent pleural thickening, air bronchograms, subpleural lines, bronchus distortion, bronchiectasis, vacuolar retraction sign, and halo sign. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have been reported rarely.[560] Ground-glass opacity has the highest diagnostic performance for COVID-19 pneumonia, followed by ground-glass opacity plus consolidation, and consolidation only.[561] • Patients with Omicron variants of SARS-CoV-2 were less likely to be CT-positive compared with those infected with non-Omicron variants. Patients with Omicron variants typically had lesions located in the center of the lung or in a single lobe. They were less likely to have bilateral lesions, crazy-paving pattern, linear opacity, and vascular enlargement, but were more likely to have bronchial wall thickening. The distribution of lesions was more extensive (bilateral and multilobe involvement) in patients with non-Omicron variants.[558] • Pregnant women appear to present more commonly with more advanced CT findings compared with the general adult	**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**

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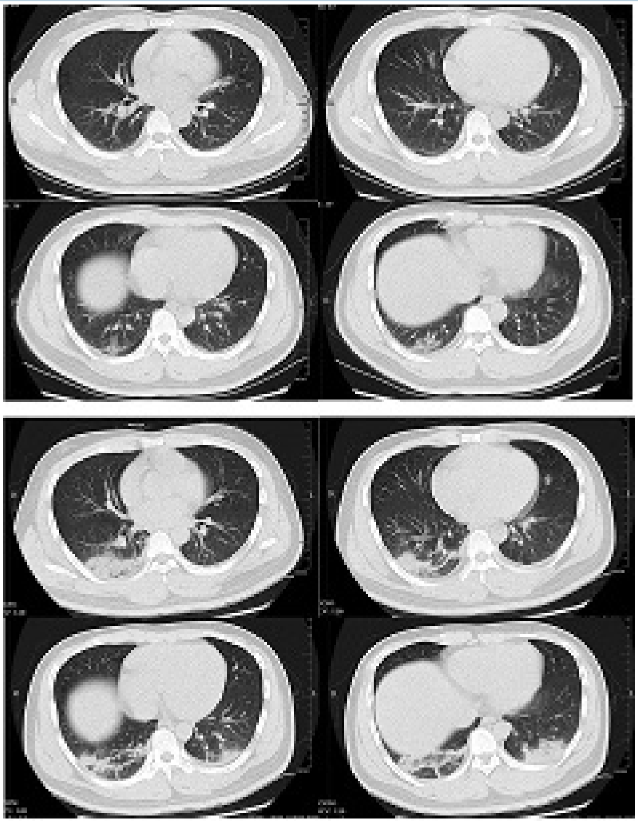
Test	Result
population; however, results are similar to those in the general adult population.[564] • Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity, nonspecific patchy shadows, areas of consolidation, infected nodules, and a halo sign. Abnormalities are more common in multiple lobes and are predominantly bilateral. Pleural effusion is rare.[565] [642] Ground-glass opacity and peribronchial thickening were the most prevalent findings in infants younger than 1 year of age.[566] Accuracy appears to be lower among children; however, there are limited data in this population.[548] • Chest CT 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.[560] • Chest CT is moderately sensitive (70%) and highly specific (90%) for the diagnosis of COVID-19.[551] Pooled results found that chest CT correctly diagnosed COVID-19 in 87% of people who had the disease. However, it incorrectly identified COVID-19 in 21% 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.[547] 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.[552] [553] The simultaneous presence of ground-glass opacity and other features of viral pneumonia had optimum	

Test	Result
performance in the detection of COVID-19 (sensitivity 90% and specificity 89%).[562] •  *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	
lung ultrasound • 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.[544] • Ultrasound is sensitive but not specific for the diagnosis of COVID-19. Pooled results found that lung ultrasound correctly diagnosed COVID-19 in 87% of people with the disease. However, it incorrectly diagnosed COVID-19 in 24% 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.[547] It may also be useful for triage in the emergency department.[643] • 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.[568] 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, repeatability during follow-up, may be more readily available in resource-limited settings, and is safe in pregnant women and children. However, it also has some limitations	**B-lines; pleural abnormalities**

Test	Result
(e.g., it is unable to discern chronicity of a lesion) and other imaging modalities may be required.[569] [570] [571] • 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).[572] Lung ultrasound score may play a role in prognosis.[573] • [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas] (https://www.bsti.org.uk/media/resources/files/Lung_US_print_out_and_scoring_proforma.pdf)	
serology • Cannot be used as a standalone diagnostic for acute infections, and should not be used to establish the presence or absence of acute infection; however, may be useful in various settings.[439][507] • 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.[505] [506] • The World Health Organization (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. 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.[439] • The Infectious Diseases Society of America (IDSA) recommends against using serologic testing to diagnose infection during the first 2 weeks following symptom onset or to provide evidence of infection in symptomatic patients with a high clinical suspicion and repeatedly negative molecular tests. Serologic testing may be used to assist with the diagnosis of multisystem inflammatory syndrome in children or when evidence of previous infection is desired.[507] • A Cochrane review found that antibody tests could be a useful tool for patients in whom molecular- or antigen-based tests have failed to detect SARS-CoV-2 virus, including in those with ongoing symptoms of acute infection (from week 3 onwards) or those presenting with post-acute sequelae. Test sensitivity is too low during the first week since the onset of symptoms.[543] • 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%. 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.[502] • For detailed information on testing limitations and evidence, see Diagnostic approach . • 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.[508] Evidence does not support their use.[509] • [BMJ practice pointer: testing for SARS-CoV-2 antibodies] (https://www.bmj.com/content/370/bmj.m3325)	**positive for SARS-CoV-2 virus antibodies; seroconversion or a rise in antibody titers in paired sera**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Community-acquired pneumonia	• 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.[644]	• Blood or sputum culture or molecular testing: positive for causative organism. • RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible). • CT chest: centrilobular nodules, mucoid impactions.[645]
Influenza infection	• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. In general, upper respiratory tract symptoms are more common with influenza.[646] Rhinorrhea, sore throat, myalgia, headache, and dyspnea are more common. Fever is less common.[647] [648] New-onset smell and/or taste disorders were less common in a case-control study.[649] • More common in children.[650] 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.[651] • Coinfection is possible, but is not significantly associated with mortality.[652] Coinfection is higher in children and critically ill patients.[653]	• 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.[647] • CT chest: there is evidence that CT can be used to help differentiate between influenza and COVID-19. COVID-19 patients are more likely to have ground-glass opacities, reverse halo signs, crazy-paving sign, vascular enlargement, and interlobular septal thickening, but less likely to have pleural effusion.[654] • Inflammatory markers and coagulation screen: there is evidence that inflammatory markers (lactate dehydrogenase, erythrocyte sedimentation rate, C-reactive protein) and coagulation parameters are not as high in patients with influenza compared with COVID-19.[655]
Common cold	• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs	• RT-PCR: positive for causative organism; negative for SARS-CoV-2 viral RNA (coinfections are possible).

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Condition	Differentiating signs / symptoms	Differentiating tests
	and symptoms. However, fever is less common with the common cold, and headache, rhinorrhea, myalgia, and sore throat are more common. Patients may have a greater number of general symptoms.[648]	
Respiratory syncytial virus (RSV) infection	• Primarily affects children age <5 years.[461] • History of exposure to RSV. • Seasonal outbreaks during winter (may vary between regions). • Increased work of breathing, wheeze, apnea, or poor feeding may be noted in infants.	• RT-PCR: positive for respiratory syncytial virus RNA; negative for SARS-CoV-2 viral RNA (coinfections are possible).
Other viral or bacterial respiratory infections	• 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	• Differentiating COVID-19 from aspiration pneumonia is not usually possible from signs and symptoms.	• RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible). • CT chest: difficult to distinguish on CT; however, anterior lung involvement may be more suggestive of COVID-19 pneumonia.[656]
Pneumocystis jirovecii pneumonia	• Differentiating COVID-19 from pneumocystis jirovecii pneumonia is not usually possible from signs and symptoms. However, patients with pneumocystis jirovecii pneumonia 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.[645]

Condition	Differentiating signs / symptoms	Differentiating tests
Avian influenza A (H5N1) virus infection	• Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in/travel to an area when avian influenza is endemic.	• RT-PCR: positive for H5N1 viral RNA.
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. However, the clinical course of MERS is usually more severe and the case fatality rate is higher.	• Reverse-transcriptase polymerase chain reaction (RT-PCR): positive for MERS-CoV viral RNA.
Avian influenza A (H7N9) virus infection	• Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in/travel to an area when avian influenza is endemic. • No human cases have been reported to the World Health Organization (WHO) since 2019.	• RT-PCR: positive for H7-specific viral RNA.
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	• Symptoms of COVID-19 and neutropenic sepsis may be difficult to differentiate at initial presentation. 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.	• CBC: neutropenia. • RT-PCR: negative for SARS-CoV-2 viral RNA.

Condition	Differentiating signs / symptoms	Differentiating tests
	• Patients with febrile neutropenia are at increased risk of COVID-19.[657]	
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.[658]	• RT-PCR: negative for SARS-CoV-2 viral RNA. • Other differentiating tests depend on the suspected diagnosis.

Criteria

World Health Organization (WHO): COVID-19 disease severity classification[444]

Mild illness

- Symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia.

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 (SpO_2) ≥90% on room air.
- Children: 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) plus one of the following:
  - Respiratory rate >30 breaths/minute
  - Severe respiratory distress
  - SpO_2 <90% on room air
- Children: clinical signs of pneumonia (i.e., cough or difficulty in breathing plus fast breathing or chest wall indrawing) plus at least one of the following:
  - SpO_2 <90%
  - Very severe chest indrawing, grunting, central cyanosis, or presence of any other general danger sign (i.e., inability to breastfeed or drink, lethargy or unconsciousness, or convulsions)

- 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.

World Health Organization (WHO): hospitalization risk for patients with nonsevere disease[406]

Several recommendations for people with nonsevere disease, specifically for the use of antiviral drugs (i.e., nirmatrelvir/ritonavir, molnupiravir, remdesivir), are stratified by the likelihood of hospital admission. The criteria for deciding whether a patient is at high, moderate, or low risk of hospitalization are detailed below.

- High risk (6%) of hospitalization
  - Diagnosed immunodeficiency syndromes.
  - History of solid organ transplant and receiving immunosuppressants.
  - Autoimmune illness and receiving immunosuppressants.
- Moderate risk (3%) of hospitalization
  - Age ≥65 years.
  - Obesity.
  - Diabetes and/or chronic cardiopulmonary disease.
  - Chronic kidney or liver disease.
  - Active cancer.
  - Disabilities.
  - Comorbidities of chronic disease.
- Low risk (0.5%) of hospitalization
  - Not at moderate or high risk of hospitalization (most patients are low risk).

Infectious Diseases Society of America (IDSA): disease severity definitions[401]

Mild-to-moderate illness

- Patients with a SpO_2 >94% not requiring supplemental oxygen.

Severe illness

- Patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.

Critical illness

- Patients on mechanical ventilation and extracorporeal mechanical oxygenation (ECMO).
- Includes end-organ dysfunction as is seen in sepsis/septic shock. The most commonly reported form of end-organ dysfunction is acute respiratory distress syndrome (ARDS).

Case definitions

Various case definitions are available:

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- [WHO: public health surveillance for COVID-19 – interim guidance] (https://www.who.int/publications/i/item/who-2019-nCoV-surveillanceguidance-2020.7)
- [CDC: coronavirus disease 2019 (COVID-19) 2023 case definition] (https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2023)
- [ECDC: case definition for COVID-19] (https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition)

Screening

Management of contacts

Definition of a contact

- The World Health Organization (WHO) defines a contact as a person who has experienced any one of the following exposures to a probable or confirmed case:[659]
  - 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 determined by local health authorities based on local risk assessments
- Exposures must have occurred during the infectious period of the case, defined as follows:[659]
  - Exposure to a symptomatic case: 2 days before and 10 days after symptom onset of the case, plus 3 days without symptoms or 3 days with improving symptoms, for a minimum period of 13 days after symptoms onset.
  - Exposure to an asymptomatic case: 2 days before and 10 days after the date on which the sample that led to confirmation was taken.
- Consult your local public health authority for more information as definitions may vary.

Quarantine periods for contacts

- The WHO recommends the following.[659]
  - Contacts who have been vaccinated (competing the primary series or with a booster dose) or previously infected in the last 90 days do not need to quarantine. However, if the contact develops symptoms within 14 days after their last exposure to a case, appropriate testing needs to be performed as soon as possible (quarantine is recommended while awaiting the test result).
  - Contacts at high risk (e.g., older age, multiple comorbidities, immunocompromised, pregnant, working in high-risk setting) and those living in high-risk settings who have not completed a primary series or received a booster vaccine dose, or who have not reported a previous infection in the last 90 days, should quarantine for 10 days. Quarantine can be shortened to 5 days if the contact tests negative on day 5 and presents no symptoms.
  - Quarantine periods of 14 days may be recommended if a new variant of concern or other priority situation emerges.
- In the UK, contacts are not required to self-isolate. However, it is recommended that they avoid contact with anyone who is at higher risk of severe disease (despite vaccination), limit close contact with people outside their household (especially in crowded, enclosed, or poorly ventilated spaces), and wear a well-fitting face covering if they do need to have close contact with others.[660]

    - [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#what-to-do-if-you-have-a-positive-covid-19-test-result)
- In the US, current respiratory guidance should be followed.
    - [CDC: preventing spread of respiratory viruses when you're sick] (https://www.cdc.gov/respiratory-viruses/prevention/precautions-when-sick.html)
- Consult your local public health authority for more information as definitions may vary.

Screening of asymptomatic populations

Widespread screening of asymptomatic people is not recommended in most countries.

- The WHO 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.[493]
- Consult your local public health authority for more information as recommendations may vary.

Drive-through screening centers

Drive-through screening centers were set up in some countries for safer and more efficient screening. The testee did not leave their car throughout the entire process, which included registration and questionnaire, exam, specimen collection, and instructions on what to do after. This method had the advantage of increased testing capacity and prevention of cross-infection between testees in the waiting space.[661]

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.[662] [663] [664]

Approach

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

Key recommendations

- Consider whether the patient can be managed at home. Most patients with asymptomatic or nonsevere disease can be managed at home.[669] Provide symptom relief as necessary, including treatments for fever or cough.[405] Consider antiviral treatment for patients with nonsevere disease who are at moderate to high risk of hospitalization.[405] [406]
- Most patients with severe or critical disease require hospital admission.[670] Assess adults for frailty on admission.[405] 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.
- Start supportive care according to the clinical presentation. This might include symptom relief, 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.[405] [444]
- Consider empiric antibiotics if there is clinical suspicion of a secondary bacterial infection. 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.[405] [444]
- Consider systemic corticosteroid therapy 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.[401] [405] [406]
- Consider the antiviral remdesivir in patients with severe disease. Low-certainty evidence suggests that remdesivir possibly reduces mortality, and moderate-certainty evidence suggests that remdesivir probably reduces the need for mechanical ventilation.[401] [405] [406]
- Consider an interleukin (IL)-6 inhibitor (tocilizumab or sarilumab) and/or a Janus kinase (JAK) inhibitor (baricitinib) in patients with severe or critical disease. High-certainty evidence suggests that IL-6 inhibitors reduce mortality and the need for mechanical ventilation. High-certainty evidence suggests that baricitinib reduces mortality, and moderate-certainty evidence suggests that it probably reduces the duration of mechanical ventilation.[401] [405] [406]
- Discontinue transmission-based precautions and release patients from the care pathway according to your local guidance.
- 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:

- [WHO: home care for patients with suspected or confirmed COVID-19 and management of their contacts] (https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts)

Guidance on when to stop isolation varies widely across locations.

- Isolation periods, if applicable, may depend on various factors including 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 (WHO) recommends 10 days of isolation for symptomatic patients, and 5 days of isolation for asymptomatic patients (based on very low-certainty evidence). Rapid antigen testing may be used to reduce the period of isolation.[444]
- Some countries now recommend isolation periods as short as 5 days to 7 days, and some no longer recommend an isolation period at all.
- Consult guidance from your local public health authority for more information.

Mild to moderate (nonsevere) COVID-19

The majority of patients have mild to moderate illness that does not warrant medical intervention or hospitalization, depending on the circulating SARS-CoV-2 variant. The pooled proportion of nonsevere illness in people infected with the Omicron variant was 98%, and the pooled proportion of asymptomatic infection was 25% (proportions varied depending on vaccination status).[445] For disease severity definitions, see Criteria .

Location of care

- Manage patients in a healthcare facility, in a community facility, or at home according to guidance from your local public health authority. Home management can be considered in most patients, with telemedicine or remote visits as appropriate. Consider managing patients at high risk of deterioration in a healthcare facility.[444][669]
    - Observational evidence suggests that implementation of an early home treatment algorithm/ remote patient monitoring program reduced the risk of hospitalization, intensive care unit admission, and length of hospital stay.[671] [672]
- The decision to manage patients at home requires careful clinical judgment and should be informed by an assessment of the patient's home environment to ensure that:[669]
    - 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.

Symptom management

- Fever and pain: acetaminophen or ibuprofen are recommended.[405] 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, and follow your local guidelines for treating acute cough.[405]
- Olfactory dysfunction: consider treatment (e.g., olfactory training, intranasal corticosteroids) if olfactory dysfunction persists beyond 2 weeks. Often it improves spontaneously and does not require specific treatment.[673] [674]
    - A Cochrane review found there is very limited evidence regarding the efficacy and harms of different interventions for preventing or treating persistent olfactory dysfunction following infection. The only evidence available is for intranasal corticosteroids (for prevention), and this is of very low certainty, so no conclusions could be drawn.[675] [676]

    - A systematic review and meta-analysis found that there were no significant differences in the improvement of olfactory scores with either intranasal or oral corticosteroids plus olfactory training compared with olfactory training alone. Olfactory function was significantly improved after olfactory training.[677] Olfactory training alone has been found to produce significant improvements in chronic olfactory dysfunction after COVID-19; adherence to the protocol and longer durations of treatment (typically ≥3 months) improve treatment outcomes.[678]

Supportive care

- 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.[405]
- Advise patients to improve air circulation by opening a window or door.[405]

Antivirals

- Antiviral agents are approved or have an emergency-use authorization in most countries. Options include:
    - Nirmatrelvir/ritonavir: nirmatrelvir is an oral SARS-CoV-2 protease inhibitor. It is administered with a low dose of ritonavir to slow the hepatic metabolism of nirmatrelvir and increase the plasma concentration of nirmatrelvir to a therapeutic level.
    - Molnupiravir: an oral SARS-CoV-2 nucleoside analog.
    - Remdesivir: an intravenous RNA polymerase inhibitor.
- The WHO strongly recommends nirmatrelvir/ritonavir in patients with nonsevere disease who are at high risk of hospitalization, and conditionally recommends nirmatrelvir/ritonavir in patients with nonsevere disease who are at moderate risk of hospitalization. It suggests the use of molnupiravir or remdesivir in patients with nonsevere disease who are at high risk of hospitalization if nirmatrelvir/ritonavir is not available, but suggests against the use of these agents in patients who are at moderate risk of hospitalization. Antiviral therapy is not recommended in patients who are at low risk of hospitalization (most patients). For risk definitions, see "World Health Organization (WHO): hospitalization risk for patients with nonsevere disease" in Criteria .[406] [679] [680]
    - 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. However, it does have significant and complex drug-drug interactions.
    - The recommendation to use nirmatrelvir/ritonavir is based on high-certainty evidence that suggests nirmatrelvir/ritonavir likely reduces hospital admission, and moderate- to high-certainty evidence that suggests it may reduce mortality depending on the patient's risk of hospitalization.
    - The recommendation to use remdesivir is based on moderate-certainty evidence that suggests remdesivir probably reduces hospital admission and reduces mortality and mechanical ventilation.
    - The recommendation to use molnupiravir is based on moderate-certainty evidence that suggests molnupiravir probably reduces hospital admission, time to symptom resolution, and mortality.
- In the UK, the National Institute for Health and Care Excellence (NICE) recommends nirmatrelvir/ritonavir or molnupiravir for adults who do not need supplemental oxygen, and have an increased risk for progression to severe disease.[405] [681]

    - Molnupiravir is only recommended if the patient has 1 or more risk factors for progression to severe disease, and both nirmatrelvir/ritonavir and sotrovimab are contraindicated or unsuitable.[682]
- In the US, the Infectious Diseases Society of America (IDSA) recommends nirmatrelvir/ritonavir or remdesivir as the preferred treatment options in patients with mild to moderate disease who are at high risk for progression to severe disease.[401]
    - Molnupiravir is recommended only in patients who have no other treatment options (i.e., nirmatrelvir/ritonavir or remdesivir).
- Treatment should be initiated as soon as possible after diagnosis, ideally within 5 days of symptom onset for nirmatrelvir/ritonavir or molnupiravir, or within 7 days of symptom onset for remdesivir.[401] [405] [406]
    - Logistical constraints may make it difficult to administer remdesivir in some outpatient settings as it requires administration via intravenous infusion.
- Antivirals may not be recommended in children, pregnant women, or breastfeeding women.[401] [405] [406] However, recommendations in guidelines vary, and you should consult your local guidelines and drug information source.
- Cases of virologic rebound (i.e., recurrent positive polymerase chain reaction result) and the recurrence of symptoms have been reported after antiviral treatment. However, it appears to be mild and self-limited. Virologic rebound was more common in patients taking nirmtarelvir/ritonavir compared with untreated patients, but was also reported in patients taking molnupiravir.[683]
- There are data that indicate that mutations associated with nirmatrelvir resistance have been identified, particularly in immunocompromised patients. However, the data suggest a low risk of significant drug resistance with current SARS-CoV-2 variants and antiviral usage patterns.[684]
- Evidence for the use of antivirals in patients with nonsevere disease is limited.
    - 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 trial.[685] However, the phase 2/3 EPIC-SR trial found that time to sustained alleviation of all signs and symptoms did not differ significantly between nirmatrelvir/ritonavir and placebo, regardless of vaccination status, in patients who were symptomatic (nonhospitalized) and at standard or high risk for severe disease.[686] Meta-analyses have found that nirmatrelvir/ritonavir reduced the risk of emergency department visits, hospitalization, intensive care unit admission, oxygen requirement, and mortality. However, large-scale randomized controlled trials are required to confirm these findings.[687] [688] One systematic review found that nirmatrelvir/ritonavir reduced the risk of mortality and hospitalization in older patients (moderate-certainty evidence), but did not improve the outcomes of mortality and hospitalization in patients age <65 years (low-certainty evidence).[689] A living systematic review and network meta-analysis found that nirmatrelvir/ritonavir is probably the best treatment at reducing hospital admission compared with standard care (moderate-certainty evidence), but may not reduce symptom duration.[690] A Cochrane review found that nirmatrelvir/ritonavir may reduce the risk of all-cause mortality and hospital admission or death within 28 days in unvaccinated outpatients with previous infection who were at high risk with symptom onset within 5 days and infected with the Delta variant (low-certainty evidence from one trial). Very low-

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certainty evidence exists regarding the effects on all-cause mortality and viral clearance in unvaccinated inpatients with mild to moderate infection caused by the Omicron variant.[691]
- Molnupiravir was found to reduce the risk of hospitalization or death by 31% (absolute risk reduction from 9.7% to 6.8%) in the 29 days after use compared with placebo in nonhospitalized, unvaccinated, at-risk adults in the phase 3 MOVe-OUT trial.[692] However, the PANORAMIC trial found that molnupiravir did not reduce the risk of hospitalization or death among high-risk vaccinated adults in the community compared with placebo, although it did reduce time to recovery.[693] Meta-analyses are conflicting. Some meta-analyses show no significant effect on reducing mortality or hospitalization with molnupiravir.[694] [695] However, others show that molnupiravir has a significant impact on reducing mortality and hospitalization.[696] [697] A living systematic review and network meta-analysis found that molnupiravir may reduce hospital admission compared with standard care (low-certainty evidence), and probably reduces symptom duration (high-certainty evidence).[690] Limited evidence suggests that use of molnupiravir may be contributing to the evolution of the SARS-CoV-2 virus, but further research is required.[698]
- Remdesivir was found to reduce the risk of hospitalization or death by 87% compared with placebo in nonhospitalized high-risk adults in a randomized, double-blind, placebo-controlled trial.[699] A living systematic review and network meta-analysis found that remdesivir probably reduces hospital admission compared with standard care (moderate-certainty evidence), but may not reduce symptom duration.[690]
- When comparing nirmatrelvir/ritonavir and molnupiravir, nirmatrelvir/ritonavir demonstrated superiority to molnupiravir in terms of all-cause mortality and hospitalization rate in one systematic review and meta-analysis. The incidence of adverse events was higher with nirmatrelvir/ritonavir, but no significant difference was observed between the two drugs in terms of adverse events that led to treatment discontinuation.[700]

Monoclonal antibodies

- Monoclonal antibodies may be approved or have an emergency-use authorization in some countries.
  - Monoclonal antibodies bind to nonoverlapping epitopes of the receptor-binding domain of the spike protein to block virus entry into host cells.
  - Options may include bebtelovimab, tixagevimab/cilgavimab, casirivimab/imdevimab, sotrovimab, bamlanivimab/etesevimab, and regdanvimab, depending on your location.
  - Outpatient administration in specialized clinics is required as these agents are administered parenterally, which may limit their feasibility.[406]
  - 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.
- Choice of monoclonal antibody depends on availability, as well as clinical and contextual factors including information about efficacy with different SARS-CoV-2 variants and subvariants.[405] [406]
  - Check your local guidance for information about whether a particular monoclonal antibody is effective against current circulating SARS-CoV-2 variants and subvariants.
  - Treatment should be started as soon as possible and within 7 days of symptom onset.
- Guideline recommendations vary.

- The WHO strongly recommends against the use of sotrovimab and casirivimab/imdevimab for patients with nonsevere disease, as there is evidence of a reduction in effectiveness against currently circulating variants of SARS-CoV-2 and their subvariants. The agency makes no recommendations for other monoclonal antibodies, and recommends the use of antivirals instead (see above).[406] [679] [680]
- In the UK, NICE recommends sotrovimab as an option for treating patients ≥12 years of age and ≥40 kg body weight who do not need supplemental oxygen, who have an increased risk for progression to severe disease, and for whom nirmatrelvir/ritonavir is contraindicated or unsuitable.[405] [681] Tixagevimab/cilgavimab is not recommended.[701]
- In the US, IDSA does not currently recommend the use of monoclonal antibodies for the treatment of COVID-19.[401]

- 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. Casirivimab/imdevimab decreases the risk of infection and development of clinical symptoms (high-certainty evidence). Bamlanivimab decreases the risk of infection (moderate-certainty evidence). These findings only apply to unvaccinated people, and are only applicable to variants prevailing during the study.[702]
  - A systematic review and meta-analysis of 27 randomized controlled trials found that monoclonal antibodies had limited effects on most of the outcomes in nonhospitalized patients with the certainty of evidence ranging from very low to moderate for most outcomes. Monoclonal antibodies reduced hospitalization, but there were no effects on mortality.[703]

Antimicrobials

- Consider empiric antibiotics in patients with nonsevere disease only if there is clinical suspicion of secondary bacterial infection. Antibiotics are not recommended if there is a low clinical suspicion of concurrent bacterial infection.[405] [444]
  - Start treatment as soon as possible, and refer to local guidelines for choice of regimen.
  - Do not offer an antibiotic for preventing secondary bacterial pneumonia.
- Advise patients to seek medical help without delay if their symptoms do not improve, or worsen rapidly or significantly.[405]
  - 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.

Monitoring

- Closely monitor patients (particularly those with risk factors for severe illness) for signs and symptoms of disease progression. Advise patients 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.[405] [444]
- 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] in adults, Pediatric Early Warning Scores [PEWS] in children).[405]

- One 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.[480]

Corticosteroids

- A living systematic review and network meta-analysis found that systemic corticosteroids may reduce hospital admission compared with standard care (low-certainty evidence), and probably reduce symptom duration (moderate-certainty evidence).[690]
- However, 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.[401] [405] [406]

Antithrombotic therapy

- Guidelines published by the US Anticoagulation Forum 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. Patients on antithrombotic therapy prior to their diagnosis should continue treatment, unless a significantly elevated risk of bleeding has developed.[704]
- One Cochrane review found that prophylactic anticoagulation results in little or no difference in the need for hospitalization, major bleeding, deep vein thrombosis, all-cause mortality, or adverse events compared with placebo or no treatment in nonhospitalized patients (low- to moderate-certainty evidence), but may reduce the incidence of pulmonary embolism and venous thromboembolism.[705] In people with mild disease, antiplatelet agents may result in little to no difference in 45-day mortality and serious adverse events, but may slightly reduce thrombotic events (low-certainty evidence).[706]

Highest-risk clinical groups

- A UK advisory group has generated a list of conditions or cohorts who are at highest risk of serious illness from COVID-19 in the community, and who would therefore benefit from treatments (e.g., antivirals, monoclonal antibodies). This list may be used when considering the use of these treatments in adults, and includes the following: Down syndrome and other genetic disorders; solid cancers; hematologic diseases and recipients of hematologic stem cell transplants; renal and liver diseases; solid organ transplant recipients; immune-mediated inflammatory disorders; respiratory diseases; immune deficiencies; HIV/AIDS; and rare neurologic and severe complex life-limiting neurodisability conditions.[707] Definitions may vary across other guidelines.

A living network meta-analysis that summarizes the available evidence for COVID-19 treatments is available:

- [COVID-19 LNMA (living network meta-analysis)] (https://www.covid19lnma.com)

Severe COVID-19

Patients with severe disease are at risk of rapid clinical deterioration. For disease severity definitions, see Criteria .

Location of care

- Most patients with severe disease require management in an appropriate healthcare facility under the guidance of a specialist team.[670]
  - The estimated length of hospital stay is more than 10 days (mean 15 days). However, the duration depends on various factors including age, country/region, and available resources.[708]

Assessment of frailty

- 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.dal.ca/sites/gmr/our-tools/clinical-frailty-scale.html) 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.[405]
- Evidence for the use of the CFS in COVID-19 is evolving despite limitations in the reporting on its application in practice.[709]
  - Patients with a score between 4 and 9 had significantly increased mortality compared with those with a score of 1-3 in one systematic review and meta-analysis.[710] Each 1-point increase in score was associated with a 12% increase in mortality.[711] However, another systematic review and meta-analysis found that there was no difference in short-term mortality between frail and nonfrail patients.[712]
  - A more nuanced understanding of frailty and outcomes is needed, and caution is required in placing too much emphasis on the influence of frailty on the prognosis of older people.[713]

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 hypoxemia.[444]
  - There is no evidence of benefit for oxygen therapy in patients with COVID-19 in the absence of hypoxemia.[714]
- Target SpO_2 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 SpO_2 >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.[444]
  - Some guidelines recommend that SpO_2 should be maintained no higher than 96%.[715]
  - Some centers may recommend different 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 in severely ill patients who require supplemental oxygen.[444]
  - Awake prone positioning reduced the risk of endotracheal intubation compared with usual care. However, it did not significantly reduce mortality, ventilator-free days, length of stay in the intensive care unit or hospital, or escalation of oxygen modality. Adverse events were uncommon.[716]

- Monitor patients closely for signs of progressive acute hypoxemic respiratory failure. Patients who continue to deteriorate despite standard oxygen therapy may require advanced oxygen/ventilatory support.[715]
- The WHO recommends HFNO, continuous positive airway pressure (CPAP), or noninvasive ventilation (helmet or face mask interface) in hospitalized patients with severe disease and acute hypoxemic respiratory failure not needing emergent intubation, rather than standard oxygen therapy. Choice depends on factors such as availability of devices and the supply of oxygen, personal comfort and experience, and patient-specific considerations (e.g., claustrophobia with CPAP or noninvasive ventilation masks, nasal discomfort with HFNO).[444]
  - Helmet bilevel positive airway pressure (BiPAP) was associated with a significantly lower intubation risk compared with HFNO and standard oxygen therapy in patients with moderate to severe disease in one meta-analysis of randomized controlled trials. Helmet BiPAP was also associated with a shorter stay in the intensive care unit compared with standard oxygen therapy. No significant differences in mortality were identified between helmet BiPAP, HFNO, standard oxygen therapy, and CPAP.[717]

Symptom management and supportive care

- Fluids and electrolytes: use cautious fluid management according to local guidelines. Correct any electrolyte or metabolic abnormalities, such as hyperglycemia or metabolic acidosis, according to local guidelines.[718]
- Fever and pain: acetaminophen or ibuprofen are recommended.[405] 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, and follow your local guidelines for treating acute cough.[405]
- 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).[405]
- Anxiety, delirium, and agitation: identify and treat any underlying or reversible causes.[405]
  - Nonpharmacologic interventions are the mainstay for the management of delirium when possible, and prevention is key.[719]
- 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.[720]

Venous thromboembolism (VTE) prophylaxis

- Assess bleeding risk: assess the patient's risk of bleeding as soon as possible after admission, or by the time of the first attending physician review, using a suitable risk assessment tool.[405]
  - If the patient is already on anticoagulation for another underlying condition, continue the current treatment dose of the anticoagulant, unless contraindicated or there is a change in clinical circumstances (e.g., bleeding develops or risk of bleeding increases).[405][704] 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.[405]
  - A systematic review and meta-analysis found that the use of oral anticoagulation prior to hospital admission was not associated with a reduced risk of intensive care unit admission and mortality. However, the review acknowledged that further trials are needed.[721]
- Start VTE prophylaxis: start prophylaxis in all hospitalized patients, provided that there are no contraindications.[405][704][722] Start as soon as possible (within 14 hours of admission).[405]

    - A Cochrane review found that anticoagulants may reduce all-cause mortality compared with no anticoagulants, but the evidence is very uncertain.[723]
    - 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.[724]
- Choice of anticoagulant: low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options.[405] [704] [722] Low molecular weight heparin is preferred over unfractionated heparin and fondaparinux, unless contraindicated.[405] However, choice of anticoagulant may also depend on local guidelines.
    - There is no high-certainty evidence comparing types of anticoagulants, but low molecular weight heparin and unfractionated heparin have been used in most studies.[725]
    - A meta-analysis found that low molecular weight heparin was associated with decreased intensive care unit admission, mechanical ventilation, hospital stay, and mortality compared with unfractionated heparin in hospitalized patients, and there was no difference in the incidence of bleeding.[726]
    - There is limited evidence that direct oral anticoagulants (factor Xa inhibitors) are more effective than low molecular weight heparin in preventing VTE in hospitalized patients who are not acutely ill. However, guidelines do not recommend these agents, and further randomized controlled trials are needed.[727]
    - Consult a specialist for guidance on the choice and dose of anticoagulant in special patient populations (e.g., children, pregnant and breastfeeding women, hepatic or renal impairment, active cancer).
- Dose of anticoagulant: recommendations vary and you should consult your local guidance.
    - The WHO conditionally recommends prophylaxis doses of heparin (unfractionated heparin or low molecular weight heparin) instead of intermediate or therapeutic doses for severe disease, except for patients with an established indication for therapeutic anticoagulation.[406]
    - In the UK, NICE recommends prophylaxis doses of low molecular weight heparin. However it also makes a conditional recommendation to consider treatment doses of low molecular weight heparin in those who may benefit. 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.[405]
    - In the US, the American Society of Hematology (ASH) suggests using therapeutic-intensity anticoagulation over prophylactic-intensity anticoagulation, and prophylactic-intensity anticoagulation over intermediate-intensity anticoagulation, in patients with COVID-19-related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation. However, an individualized assessment of the patient’s risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. Lower-intensity anticoagulation may be preferred for patients at low thrombotic risk and high bleeding risk. These suggestions are based on very uncertain evidence.[725] The Anticoagulation Forum recommends therapeutic-intensity anticoagulation for noncritically ill patients who are not high risk for bleeding.[704] Prophylactic-dose anticoagulation is recommended by some US guidelines.[722]

- 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).[723]

- Duration of treatment: anticoagulation is generally continued until hospital discharge. Routine post-discharge VTE prophylaxis is generally not recommended, except in certain high-risk patients or if another indication for VTE prophylaxis exists.[704][722] [725] However, in the UK, NICE recommends treatment for a minimum of 7 days, including after discharge, if standard prophylaxis doses of heparin are used.[405] If therapeutic doses of heparin are used, the recommended treatment duration is 14 days or until hospital discharge, whichever is sooner.[405] Some guidelines recommend that oral rivaroxaban (a direct oral anticoagulant) may be considered for post-discharge VTE prophylaxis.[704]

    - A systematic review and meta-analysis found that extended thromboprophylaxis (with either a direct oral anticoagulant or low molecular weight heparin at prophylaxis doses) administered for <35 days was significantly associated with a reduced risk of thrombosis and all-cause mortality in patients post discharge who were at high risk of thromboembolism, without increasing the risk of major bleeding.[728]

- Monitoring: monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways, according to local guidelines, if clinically suspected. See Complications .

    - If the patient’s clinical condition changes, assess the risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.[405]
    - Monitoring of clinical parameters during thromboprophylaxis depends on the anticoagulant and dose used. Consult your local protocols for more information.

Antimicrobials

- 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.[405] 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.

    - 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.[405]
    - Antibiotics are not recommended for patients with severe disease if there is a low clinical suspicion of concurrent bacterial infection.[444]
    - 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.[729]

- 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.[405]
    - 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.
- Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local guidelines.

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.[406] [679] [680]
    - This recommendation is based on moderate-quality evidence that suggests 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, NICE recommends offering dexamethasone (or an alternative such as hydrocortisone or prednisone when dexamethasone cannot be used or is unavailable) for up to 10 days (unless there is a clear indication to stop early) 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.[405]
- In the US, IDSA recommends dexamethasone (or an alternative corticosteroid if dexamethasone is not available) for 10 days or until hospital discharge in hospitalized patients with severe disease.[401]
- Evidence supports the use of corticosteroids in hospitalized patients.
    - A Cochrane review found that systemic corticosteroids probably slightly reduce all-cause mortality up to 30 days in hospitalized patients with symptomatic disease (moderate-certainty evidence), although the evidence is very uncertain about the effect on all-cause mortality up to 120 days. Evidence related to the most effective type, dose, or timing of corticosteroid is uncertain.[730]
    - A living systematic review and network meta-analysis found that corticosteroids probably reduce mortality compared with standard care.[731] [732]
    - Evidence suggests that higher doses may be superior to lower doses in reducing mortality in patients with severe or critical disease.[733] However, the RECOVERY trial found that higher-dose corticosteroids significantly increased the risk of death compared with usual care (which included low-dose corticosteroids) in hospitalized patients who required either no oxygen or simple oxygen only. The study continues to assess higher doses in hospitalized patients who require noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[734]
    - Evidence also suggests that shorter treatment courses may optimize the mortality benefit in hospitalized patients. An optimal duration of treatment was <7 days in one meta-analysis, with no additional survival benefit reported with ≥7 days of treatment.[735]

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

Antivirals

- The WHO conditionally recommends the intravenous antiviral remdesivir for 5 to 10 days in adults with severe disease. It should be initiated as soon as possible after the onset of symptoms.[406] [679] [680]
  - This recommendation is based on low-certainty evidence that suggests remdesivir possibly reduces mortality, and moderate-certainty evidence that suggests it probably reduces the need for mechanical ventilation. Moderate-certainty evidence suggests that remdesivir probably has little or no impact on time to symptom improvement. There is insufficient evidence to make a recommendation around use in children.
- In the UK, NICE recommends remdesivir as an option in hospitals in adults at high risk of serious illness, and children (ages 4 weeks to 17 years and weight ≥3 kg) who have pneumonia and need supplemental oxygen or who weigh ≥40 kg and have a high risk of serious illness.[405] [701]
- In the US, IDSA recommends remdesivir for 5 days in patients who require supplemental oxygen.[401]
- The recommended treatment course is 5 to 10 days or until hospital discharge, whichever comes first.[401] [405] [406]
  - 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. There may be no benefit in completing the full course of remdesivir if the patient progresses.[405]
- Despite guidelines recommending the use of remdesivir in patients with severe disease, evidence for its use is conflicting.
  - A Cochrane review found that remdesivir probably has little or no effect on all-cause mortality (up to 150 days) in hospitalized patients with moderate to severe disease compared with placebo or usual care (moderate-certainty evidence). Remdesivir probably increases the chance of clinical improvement up to day 28 slightly, and decreases the risk of clinical worsening within 28 days (moderate-certainty evidence).[736]
  - One systematic review of randomized controlled trials and real-world studies (including over 1.2 million participants) found that remdesivir significantly decreased all-cause mortality at 28-30 days in hospitalized patients, regardless of disease severity, SARS-CoV-2 variant, or vaccination era.[737]
  - A 1-year follow-up of hospitalized patients in a randomized controlled trial found no long-term benefits (quality-of-life or symptom outcomes) for remdesivir compared with standard of care.[738]
- Oral antivirals (nirmatrelvir/ritonavir, molnupiravir) are not currently recommended in patients with severe disease. Current evidence does not support adding these drugs to standard care for hospitalized patients as they have not been associated with improved clinical outcomes.[739]

Interleukin-6 (IL-6) inhibitors

- The WHO strongly recommends a single dose of an IL-6 inhibitor (tocilizumab or sarilumab) in adults with severe disease. IL-6 inhibitors may be administered in combination with corticosteroids and JAK inhibitors, and should be initiated at the same time as corticosteroids.[406] [679] [680]

    - 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.
- In the UK, NICE recommends a single dose of tocilizumab in hospitalized adults who are having systemic corticosteroids and need supplemental oxygen or mechanical ventilation.[405] [681]
- In the US, IDSA recommends a single dose of tocilizumab (or sarilumab if tocilizumab is not available) in hospitalized patients with progressive severe disease who have elevated markers of systemic inflammation in addition to standard care (i.e., corticosteroids).[401]
- Evidence supports the use of IL-6 inhibitors.
    - A Cochrane review found that tocilizumab reduced all-cause mortality at day 28 (high-certainty evidence) compared with standard care alone or placebo. The evidence suggests uncertainty around the effect of tocilizumab on mortality after day 60. Evidence for an effect on these outcomes for sarilumab is very uncertain. Tocilizumab and sarilumab probably result in little or no increase in clinical improvement at day 28 (i.e., hospital discharge or improvement measured by trialist-defined scales) (moderate-certainty evidence). The evidence for clinical improvement after day 60 is very uncertain for both drugs.[740]
    - A living systematic review and network meta-analysis found that IL-6 inhibitors (with corticosteroids) probably reduce mortality (moderate-certainty evidence), are likely to reduce the need for mechanical ventilation (moderate-certainty evidence), and may reduce the duration of hospitalization (moderate-certainty evidence) compared with standard care.[731] [732]
    - IL-6 inhibitors may not be beneficial when used alone (without corticosteroids).[741]

Janus kinase (JAK) inhibitors

- The WHO strongly recommends an oral JAK inhibitor (baricitinib) for 14 days or until hospital discharge (whichever is first) in adults with severe disease. Baricitinib may be administered in combination with corticosteroids and IL-6 inhibitors, and should be initiated at the same time as systemic corticosteroids.[406] [679] [680]
    - This recommendation is based on high-certainty evidence that baricitinib reduces mortality, and moderate-certainty evidence that baricitinib probably reduces the duration of mechanical ventilation and the length of hospital stay. The applicability of this recommendation to children is currently uncertain.
    - The WHO recommends against using other drugs within this class (tofacitinib and ruxolitinib) 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, NICE 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. It may also be considered in children ≥2 years of age provided they meet the same criteria.[405]
- In the US, IDSA recommends baricitinib in hospitalized patients with severe disease, in addition to corticosteroid therapy. It may also be used in patients who cannot receive a corticosteroid due to a contraindication (in combination with remdesivir).[401]

- Evidence supports the use of JAK inhibitors.
    - A Cochrane review found that JAK inhibitors probably reduced all-cause mortality up to day 28 (moderate-certainty evidence) and up to day 60 (high-certainty evidence). They probably make little or no difference in improvement in clinical status or the rate of adverse events (moderate-certainty evidence). Baricitinib was the most often evaluated JAK inhibitor.[742]
    - A living systematic review and network meta-analysis found that JAK inhibitors probably reduce mortality (high-certainty evidence), reduce the duration of mechanical ventilation (high-certainty evidence), and reduce length of hospital stay (high-certainty evidence) compared with standard care.[731] [732]

Other immunomodulatory agents

- In the US, IDSA recommends intravenous abatacept or infliximab in hospitalized adults with rapidly progressing disease who are receiving systemic corticosteroids, as alternatives to baricitinib and tocilizumab (when these drugs are not available), based on low-certainty evidence.[401]
- However, other guidelines do not recommend these agents as yet.

Monoclonal antibodies

- Recommendations for monoclonal antibodies in patients with severe disease differ from the recommendations for patients with mild to moderate disease. Key international guidelines do not currently recommend monoclonal antibodies for patients with severe disease.
    - The WHO strongly recommends against the use of casirivimab/imdevimab for patients with any disease severity. The agency makes no other recommendations either for or against the use of other monoclonal antibodies in patients with severe disease.[406] [679] [680]
    - In the UK, NICE recommends not offering casirivimab/imdevimab to patients who are known or suspected to have infection caused by an Omicron variant.[405]
    - In the US, IDSA does not currently recommend the use of monoclonal antibodies for the treatment of COVID-19.[401]
- Evidence for the use of monoclonal antibodies in hospitalized patients is uncertain.
    - A systematic review and meta-analysis of 27 randomized controlled trials found that monoclonal antibodies had limited effects on most of the outcomes in hospitalized patients with the certainty of evidence ranging from very low to moderate for most outcomes. Monoclonal antibodies slightly reduced mechanical ventilation and bacteremia, but there were no effects on mortality.[703]

Monitoring

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

Palliative care

- Palliative care interventions should be integrated with curative treatment. Basic palliative care is recommended in all patients, as appropriate.[444] Follow local palliative care guidelines.
- There is 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.[743]

A living network meta-analysis that summarizes the available evidence for COVID-19 treatments is available:

- [COVID-19 LNMA (living network meta-analysis)] (https://www.covid19lnma.com)

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. For disease severity definitions, see Criteria . The overall pooled mortality rate in patients with critical illness was 34%, and 62% of patients required mechanical ventilation. Approximately 69% of these patients had comorbidities.[744]

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.[444]

Location of care

- Patients with critical disease are usually managed in an intensive/critical care unit under the guidance of a specialist team.
  - Patients admitted to intensive care units had a median length of stay of 23 days (range 12-32 days).[745] The most common reasons for admission were hypoxemic respiratory failure leading to mechanical ventilation and hypotension.[746]
- 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 intervention. 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.[405]

HFNO or noninvasive ventilation

- The WHO recommends HFNO, CPAP, or noninvasive ventilation (helmet or face mask interface) in hospitalized patients with critical disease and acute hypoxemic respiratory failure not needing emergent intubation, rather than standard oxygen therapy.[444]
  - Choice depends on factors such as availability of devices and the supply of oxygen, personal comfort and experience, and patient-specific considerations (e.g., claustrophobia with CPAP or noninvasive ventilation masks, nasal discomfort with HFNO).
  - Consider awake prone positioning in severely ill patients who require HFNO or noninvasive ventilation.
- In the UK, NICE 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.[405]
  - 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.
- 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.[747]
    - Limited evidence suggests that noninvasive ventilation reduces the need for intubation, improves resource utilization, may be associated with better outcomes, and is safe.[748]
    - 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.[749] [750]
    - 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.[751] [752]
    - HFNO may reduce intubation rate and 28-day intensive care unit mortality, and may improve 28-day ventilator-free days compared with conventional oxygen therapy in patients with acute respiratory failure. However, large-scale randomized controlled trials are necessary.[753]
    - 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.[754]
    - The HELMET-COVID trial (a multicenter randomized clinical trial) found that helmet noninvasive ventilation did not significantly reduce 28-day mortality compared with usual respiratory support (alternate use of mask noninvasive ventilation, HFNO, or standard oxygen according to clinical response) among patients with acute hypoxemic respiratory failure. However, there were several important limitations to the study, and interpretation of the findings is limited by imprecision in the effect size estimate.[755]
    - The SOHO-COVID trial (a randomized clinical trial) found that HFNO did not significantly reduce 28-day mortality compared with standard oxygen therapy among patients with respiratory failure.[756] However, 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.[757]
- Airborne precautions may be recommended for these interventions due to uncertainty about the potential for aerosolization. Consult your local guidelines.

    - However, CPAP and HFNO do not appear to be associated with significant additional air or surface viral contamination compared with supplemental oxygen.[758] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[759] A systematic review and meta-analysis found no association between HFNO and noninvasive ventilation and aerosol generation-increased airborne pathogen detection.[760]
- Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions they may require urgent endotracheal intubation.[715]
- More detailed guidance on the management of acute respiratory distress syndrome (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 with ARDS who are acutely deteriorating despite advanced oxygen/noninvasive ventilatory support measures.[444] [715]
    - 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. Outcomes appear to have improved as the pandemic has progressed.[761] However, results have not been consistent.[762]
    - Early intubation may be associated with lower all-cause mortality compared with patients undergoing late intubation. However, again, results have not been consistent.[763] [764]
- 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 suggested 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.[444][715]
    - Although some patients with COVID-19 pneumonia meet the criteria for ARDS, there has been some discussion about whether COVID-19 pneumonia is its own specific disease with atypical phenotypes. Anecdotal evidence from early in the pandemic suggested that the main characteristic of the atypical presentation was the dissociation between well-preserved lung mechanics and the severity of hypoxemia.[765] [766] [767] [768] [769] [770] However, this hypothesis was criticized.[771] [772] A systematic review and meta-analysis published in late 2022 found no evidence for distinct respiratory system static compliance-based clinical phenotypes in patients with COVID-19-related ARDS.[773]
    - 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.[774] However, some clinicians have warned that protocol-driven ventilator use may cause 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.[765] Therefore, PEEP should always be carefully titrated.[775]

- 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.[444][715] Longer durations may be feasible in some patients.[776]
    - A systematic review and meta-analysis found that there was no significant difference in mortality between prone and supine positioning, and that hospital stay was significantly higher in the prone position group. There was no difference between the two groups in terms of length of stay in the intensive care unit and days of mechanical ventilation.[777]
- Lung recruitment maneuvers are suggested, but staircase recruitment maneuvers are not recommended.[715]
- 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 and children who have severe ARDS and refractory hypoxemia despite optimizing ventilation. Taper off if there is no rapid improvement in oxygenation.[715]
    - A systematic review and meta-analysis found that inhaled pulmonary vasodilators may improve oxygenation, but showed no mortality benefit, compared with standard therapy.[778]

Extracorporeal membrane oxygenation

- Consider extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[715]
- Evidence to support the use of ECMO is limited.
    - A registry-based cohort study found that ECMO was associated with a 7.1% reduction in mortality in selected adults (i.e., PaO_2/FiO_2 <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 PaO_2/FiO_2 <80 mmHg or with driving pressures >15 cm H_2O during the first 10 days of mechanical ventilation.[779]
    - Pooled mortality rates in adults receiving ECMO ranged from 39% to 49%.[780] [781] The mortality rate in children was 26.6%.[782] Factors associated with an increased risk of mortality included older age, male sex, chronic lung disease, longer duration of symptoms, longer duration of invasive mechanical ventilation, higher driving pressure, and higher partial pressure of arterial carbon dioxide.[783]
    - There is a high risk of thrombotic and neurologic complications (e.g., circuit thrombosis, major bleeding, intracranial hemorrhage, ischemic stroke, and hypoxic ischemic brain injury) in patients on ECMO.[784] [785] [786]

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 Complications .

Symptom management and supportive care

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

VTE prophylaxis

- If not already started, start VTE prophylaxis in all hospitalized patients, provided there are no contraindications.[405] [704] [722] Choice of anticoagulant and anticoagulation dose recommendations vary, and you should consult your local guidelines.
    - The WHO conditionally recommends prophylaxis doses of heparin (unfractionated heparin or low molecular weight heparin) instead of intermediate or therapeutic doses for critical disease, except for patients with an established indication for therapeutic anticoagulation.[406]
    - In the UK, NICE 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.[405]
    - In the US, ASH suggests using prophylactic-intensity anticoagulation over intermediate- or therapeutic-intensity anticoagulation for patients with COVID-19-related critical illness who do not have suspected or confirmed VTE or another indication for anticoagulation. An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. Higher-intensity anticoagulation may be preferred for patients at high thrombotic risk and low bleeding risk. Low molecular weight heparin and unfractionated heparin have been used in most studies.[725] Other US guidelines also support the use of prophylactic-dose thromboprophylaxis for patients who are critically ill.[704] [722]
    - Recommendations for VTE prophylaxis in patients with critical disease may differ from those for severe disease (see above), and you should consult your local guidelines.
- Evidence for VTE prophylaxis 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.[787]
    - Another smaller systematic review and meta-analysis found no difference between escalated doses and standard prophylaxis dosing in terms of impact on mortality in critically ill patients. However, there was a reduced risk of pulmonary embolism in the escalated dose group.[788]
    - Other meta-analyses have confirmed the lack of mortality benefit in patients with critical disease.[789]

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.
    - This recommendation is based on moderate-quality evidence that suggests systemic corticosteroids probably reduce 28-day mortality in patients with critical disease. They also probably reduce the need for invasive ventilation.[406]
- In the US, IDSA recommends dexamethasone (or an alternative corticosteroid if dexamethasone is not available) for 10 days or until hospital discharge in critically ill patients.[401]
- See the corticosteroids section under Severe COVID-19 above for more information.

Antivirals

- Remdesivir may increase the risk of death in critically ill patients, and for this reason the WHO, NICE, and IDSA recommend against the routine use of remdesivir in patients with critical disease.[401] [405] [406]

Interleukin-6 (IL-6) inhibitors

- The WHO strongly recommends an IL-6 inhibitor (tocilizumab or sarilumab) in adults with critical disease.[406] [679] [680]
- In the UK, NICE recommends a single dose of tocilizumab in hospitalized adults who are having systemic corticosteroids and need supplemental oxygen or mechanical ventilation.[405] [681]
- In the US, IDSA recommends a single dose of tocilizumab (or sarilumab if tocilizumab is not available) in critically ill patients who have elevated markers of systemic inflammation in addition to standard care (i.e., corticosteroids).[401]
- See the IL-6 inhibitors section under Severe COVID-19 above for more information.

Janus kinase (JAK) inhibitors

- The WHO strongly recommends an oral JAK inhibitor (baricitinib) in adults with critical disease.[406] [679] [680]
- In the UK, NICE 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. It may also be considered in children ≥2 years of age provided they meet the same criteria.[405]
- In the US, IDSA recommends baricitinib in critically ill patients receiving HFNO or noninvasive ventilation (and patients receiving invasive ventilation or ECMO when IL-6 inhibitors are not available), in addition to corticosteroid therapy.[401]
- See the JAK inhibitors section under Severe COVID-19 above for more information.

Other immunomodulatory agents

- In the US, IDSA recommends intravenous abatacept or infliximab in hospitalized adults with critical disease who are receiving systemic corticosteroids, as alternatives to baricitinib and tocilizumab (when these drugs are not available), based on low-certainty evidence.[401]
- However, other guidelines do not recommend these agents as yet.

Palliative care

- Palliative care interventions should be integrated with curative treatment. Basic palliative care is recommended in all patients, as appropriate..[444] Follow local palliative care guidelines.
- There is a lack of data on palliative care in patients with COVID-19.
  - A Cochrane review found very low-certainty evidence for the efficacy of pharmacologic interventions for palliative symptom relief, and no evidence on the safety of pharmacologic interventions or safety and efficacy of nonpharmacologic interventions for palliative symptom control. More evidence is needed to guide end-of-life management.[790]
  - 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.[743]

A living network meta-analysis that summarizes the available evidence for COVID-19 treatments is available:

- [COVID-19 LNMA (living network meta-analysis)] (https://www.covid19lnma.com)

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.

Pregnant women can generally be treated with the same supportive therapies as for nonpregnant adults, taking into account the physiologic changes that occur with pregnancy. However, VTE prophylaxis recommendations may differ, and the safety of antivirals in pregnancy has not been established. Despite this, it is important that pregnant women are not denied treatment inappropriately.[791]

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.[792] [793]

Follow your local infection prevention and control procedures during labor and delivery and for newborn care. 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.[444]

A detailed discussion of the management of pregnant women is beyond the scope of this topic. Consult your local protocols for more information.

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 to moderate (nonsevere) disease		
	1st	consider home management or hospital admission
	plus	monitoring
	plus	symptom management and supportive care
	adjunct	antipyretic/analgesic
	adjunct	antimicrobials
	adjunct	antiviral
	adjunct	monoclonal antibody
severe disease		
	1st	hospital admission
	adjunct	oxygen therapy
	plus	symptom management and supportive care
	plus	venous thromboembolism (VTE) prophylaxis
	adjunct	antimicrobials
	adjunct	corticosteroid
	adjunct	antiviral
	adjunct	interleukin-6 (IL-6) inhibitor
	adjunct	Janus kinase (JAK) inhibitor
	adjunct	antipyretic/analgesic
	adjunct	palliative care
critical disease		
	1st	intensive/critical care unit admission
	plus	symptom management and supportive care
	plus	venous thromboembolism (VTE) prophylaxis
	adjunct	high-flow nasal oxygen (HFNO) or noninvasive ventilation

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	adjunct	invasive mechanical ventilation
	adjunct	inhaled pulmonary vasodilator
	adjunct	extracorporeal membrane oxygenation (ECMO)
	adjunct	corticosteroid
	adjunct	interleukin-6 (IL-6) inhibitor
	adjunct	Janus kinase (JAK) inhibitor
	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 to moderate (nonsevere) disease

1st **consider home management or hospital admission**

» Consider isolating patients with suspected or confirmed asymptomatic or nonsevere disease according to guidance from your local public health authority. For disease severity definitions, see Criteria .

» Manage patients in a healthcare facility, in a community facility, or at home, according to guidance from your local public health authority. Home management can be considered in most patients, with telemedicine or remote visits as appropriate. Consider managing patients at high risk of deterioration in a healthcare facility.[444] [669]

» Implement local infection prevention and control procedures when managing patients. Advise patients in home isolation and household members to follow appropriate infection prevention and control measures:

» [WHO: home care for patients with suspected or confirmed COVID-19 and management of their contacts] (https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts)

» Guidance on when to stop isolation varies widely across locations. Isolation periods, if applicable, may depend on various factors including circulating SARS-CoV-2 variants and patient factors (e.g., immunocompetent/immunocompromised, asymptomatic/symptomatic, disease severity). The World Health Organization (WHO) recommends 10 days of isolation for symptomatic patients, and 5 days of isolation for asymptomatic patients (based on very low-certainty evidence). Rapid antigen testing may be used to reduce the period of isolation.[444] Some countries now recommend isolation periods as short as 5 days to 7 days, and some no longer recommend isolation periods at all. Consult guidance from your local public health authority for more information.

Acute

plus **monitoring**

Treatment recommended for ALL patients in selected patient group

» Closely monitor patients (particularly those with risk factors for severe illness) for signs and symptoms of disease progression. Advise patients 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.[405] [444]

» 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] in adults, Pediatric Early Warning Scores [PEWS] in children), and respond immediately with appropriate supportive care interventions.[405]

plus **symptom management and supportive care**

Treatment recommended for ALL patients in selected patient group

» For the management of cough, advise patients to avoid lying on their back as this makes coughing ineffective, and follow your local guidelines for treating acute cough.[405]

» 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.[405]

» Advise patients to improve air circulation by opening a window or door.[405]

» Consider treatment for olfactory dysfunction (e.g., olfactory training, intranasal corticosteroids) if it persists beyond 2 weeks.[673] [674] Olfactory training alone has been found to produce significant improvements in chronic olfactory dysfunction after COVID-19; adherence to the protocol and longer durations of treatment (typically ≥3 months) improve treatment outcomes.[678] A Cochrane review found there is very limited evidence regarding the efficacy and harms of different interventions for preventing or treating persistent olfactory dysfunction following infection.

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The only evidence available is for intranasal corticosteroids (for prevention), and this is of very low certainty, so no conclusions could be drawn.[675] [676] A systematic review and meta-analysis found that there were no significant differences in the improvement of olfactory scores with either intranasal or oral corticosteroids plus olfactory training compared with olfactory training alone. Olfactory function was significantly improved after olfactory training.[677]

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.[405]

» 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 **antimicrobials**

Treatment recommended for SOME patients in selected patient group

» Consider empiric antibiotics in patients with nonsevere disease only if there is clinical suspicion of secondary bacterial infection. Antibiotics are not recommended if there is a low clinical suspicion of concurrent bacterial infection. Start treatment as soon as possible, and refer to local guidelines for choice of regimen.[405] [444] The regimen should be based on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.

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» Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.[405]

» 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.[405]

adjunct **antiviral**

Treatment recommended for SOME patients in selected patient group

Primary options

» nirmatrelvir and ritonavir: children ≥12 years of age and ≥40 kg body weight and adults (with eGFR ≥60 mL/minute): 300 mg (nirmatrelvir)/100 mg (ritonavir) orally twice daily for 5 days; children ≥12 years of age and ≥40 kg body weight and adults (with eGFR 30 to 59 mL/minute): 150 mg (nirmatrelvir)/100 mg (ritonavir) orally twice daily for 5 days; children ≥12 years of age and ≥40 kg body weight and adults (with eGFR <30 mL/minute): 300 mg (nirmatrelvir)/100 mg (ritonavir) orally as a single dose on day 1, followed by 150 mg (nirmatrelvir)/100 mg (ritonavir) once daily for 4 days
Licensing and guideline recommendations for use in children vary; check your local guidelines or drug information source for more information.

Nirmatrelvir/ritonavir is not recommended in some countries for patients with severe renal impairment (eGFR <30 mL/minute); check your local drug information source for more information. No dose adjustment is required in patients with mild to moderate hepatic impairment; use is not recommended in severe hepatic impairment.

Secondary options

» remdesivir: neonates <28 days of age and ≥1.5 kg body weight: 2.5 mg/kg intravenously as a loading dose on day 1, followed by 1.25 mg/kg every 24 hours for 2 days; children ≥28 days of age and 1.5 to <3 kg body weight: 2.5

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mg/kg intravenously as a loading dose on day 1, followed by 1.25 mg/kg every 24 hours for 2 days; children ≥28 days of age and 3 to <40 kg body weight: 5 mg/kg intravenously as a loading dose on day 1, followed by 2.5 mg/kg every 24 hours for 2 days; children ≥40 kg body weight and adults: 200 mg intravenously as a loading dose on day 1, followed by 100 mg every 24 hours for 2 days

Licensing and guideline recommendations for use in children vary; check your local guidelines or drug information source for more information. Only the lyophilized powder formulation is recommended in pediatric patients <40 kg body weight.

No dose adjustment is required in patients with any degree of hepatic or renal impairment (including patients on dialysis).

OR

» molnupiravir: adults: 800 mg orally twice daily for 5 days

No dose adjustment is required in patients with any degree of hepatic or renal impairment (including patients on dialysis).

» Consider an antiviral agent. Options include nirmatrelvir/ritonavir, molnupiravir, and remdesivir. Guideline recommendations vary.

» The World Health Organization (WHO) strongly recommends nirmatrelvir/ritonavir in patients with nonsevere disease who are at high risk of hospitalization, and conditionally recommends nirmatrelvir/ritonavir in patients with nonsevere disease who are at moderate risk of hospitalization. It suggests the use of molnupiravir or remdesivir in patients with nonsevere disease who are at high risk of hospitalization if nirmatrelvir/ritonavir is not available, but suggests against the use of these agents in patients who are at moderate risk of hospitalization. Antiviral therapy is not recommended in patients who are at low risk of hospitalization (most patients). For risk definitions, see "World Health Organization (WHO): hospitalization risk for patients with nonsevere disease" in Criteria . 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

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concerns with respect to harms than does molnupiravir, and is easier to administer than intravenous remdesivir. However, it does have significant and complex drug-drug interactions.[406] [679] [680]

» In the UK, the National Institute for Health and Care Excellence (NICE) recommends nirmatrelvir/ritonavir or molnupiravir for adults who do not need supplemental oxygen, and have an increased risk for progression to severe disease.[405] [681] Molnupiravir is only recommended if the patient has 1 or more risk factors for progression to severe disease, and both nirmatrelvir/ritonavir and sotrovimab are contraindicated or unsuitable.[682]

» In the US, the Infectious Diseases Society of America (IDSA) recommends nirmatrelvir/ritonavir or remdesivir as the preferred treatment options in patients with mild to moderate disease who are at high risk for progression to severe disease. Molnupiravir is recommended only in patients who have no other treatment options (i.e., nirmatrelvir/ritonavir or remdesivir).[401]

» Treatment should be initiated as soon as possible after diagnosis, ideally within 5 days of symptom onset for nirmatrelvir/ritonavir or molnupiravir, or within 7 days of symptom onset for remdesivir.[401] [405] [406]

» Logistical constraints may make it difficult to administer remdesivir in some outpatient settings as it requires administration via intravenous infusion.

» Evidence for the use of antivirals in patients with nonsevere disease is limited. 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 trial.[685] However, the phase 2/3 EPIC-SR trial found that time to sustained alleviation of all signs and symptoms did not differ significantly between nirmatrelvir/ritonavir and placebo, regardless of vaccination status, in patients who were symptomatic (nonhospitalized) and at standard or high risk for severe disease.[686] Meta-analyses have found that nirmatrelvir/ritonavir reduced the risk of emergency department visits, hospitalization, intensive care unit admission, oxygen requirement, and mortality. However, large-scale randomized controlled trials are required to confirm these findings.[687] [688]

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One systematic review found that nirmatrelvir/ritonavir reduced the risk of mortality and hospitalization in older patients (moderate-certainty evidence), but did not improve the outcomes of mortality and hospitalization in patients age <65 years (low-certainty evidence).[689] A living systematic review and network meta-analysis found that nirmatrelvir/ritonavir is probably the best treatment at reducing hospital admission compared with standard care (moderate-certainty evidence), but may not reduce symptom duration.[690] A Cochrane review found that nirmatrelvir/ritonavir may reduce the risk of all-cause mortality and hospital admission or death within 28 days in unvaccinated outpatients with previous infection who were at high risk with symptom onset within 5 days and infected with the Delta variant (low-certainty evidence from one trial). Very low-certainty evidence exists regarding the effects on all-cause mortality and viral clearance in unvaccinated inpatients with mild to moderate infection caused by the Omicron variant.[691] Molnupiravir was found to reduce the risk of hospitalization or death by 31% (absolute risk reduction from 9.7% to 6.8%) in the 29 days after use compared with placebo in nonhospitalized, unvaccinated, at-risk adults in the phase 3 MOVe-OUT trial.[692] However, the PANORAMIC trial found that molnupiravir did not reduce the risk of hospitalization or death among high-risk vaccinated adults in the community compared with placebo, although it did reduce time to recovery.[693] Meta-analyses are conflicting. Some meta-analyses show no significant effect on reducing mortality or hospitalization with molnupiravir.[694] [695] However, others show that molnupiravir has a significant impact on reducing mortality and hospitalization.[696] [697] A living systematic review and network meta-analysis found that molnupiravir may reduce hospital admission compared with standard care (low-certainty evidence), and probably reduces symptom duration (high-certainty evidence).[690] Limited evidence suggests that use of molnupiravir may be contributing to the evolution of the SARS-CoV-2 virus, but further research is required.[698] Remdesivir was found to reduce the risk of hospitalization or death by 87% compared with placebo in nonhospitalized high-risk adults in a randomized, double-blind, placebo-controlled trial.[699] A living systematic review and network meta-analysis found that remdesivir probably reduces hospital admission compared with standard care (moderate-certainty evidence), but may

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not reduce symptom duration.[690] When comparing nirmatrelvir/ritonavir and molnupiravir, nirmatrelvir/ritonavir demonstrated superiority to molnupiravir in terms of all-cause mortality and hospitalization rate in one systematic review and meta-analysis. The incidence of adverse events was higher with nirmatrelvir/ritonavir, but no significant difference was observed between the two drugs in terms of adverse events that led to treatment discontinuation.[700]

» Remdesivir and nirmatrelvir/ritonavir may be offered to pregnant women, if indicated. However, molnupiravir is not recommended for pregnant or breastfeeding women.[406] A pregnancy test should be performed prior to initiation of molnupiravir because animal studies have shown reproductive toxicity and it may affect bone and cartilage growth. Contraception is recommended during molnupiravir 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. The WHO recommends that pregnant or breastfeeding women may be offered nirmatrelvir/ritonavir as part of a fully informed shared decision-making process given the possible benefit and residual uncertainty regarding potential adverse effects.[406] A case series of 47 pregnant women treated with nirmatrelvir/ritonavir found that treatment was well tolerated, although there was an unexpectedly high rate of cesarean deliveries. Further larger studies are needed to evaluate for complications in pregnant women and neonates.[794]

» Remdesivir is associated with hepatotoxicity and hypersensitivity reactions. 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. 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. Bradycardia has been reported during the infusion and may

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persist past the initial infusion.[795] [796] Acute kidney injury has also been reported.

» Adverse effects with nirmatrelvir/ritonavir and molnupiravir are generally considered to be mild. However, there are limited safety data on these new medications, and all suspected adverse effects must be reported to your local pharmacovigilance program. Common adverse effects of nirmatrelvir/ritonavir include diarrhea, dysgeusia, hypertension, and myalgia. Cases of abdominal pain, anaphylaxis, hypersensitivity reactions, toxic epidermal necrolysis, and Stevens-Johnson syndrome have been reported in postmarketing surveillance.[797] Use caution in patients with preexisting liver diseases (ritonavir has been associated with elevated liver enzymes, hepatitis, and jaundice). Common adverse effects of molnupiravir include diarrhea, nausea, headache, and dizziness. Cases of virologic rebound (i.e., recurrent positive polymerase chain reaction result) and the recurrence of symptoms have been reported after antiviral treatment. However, it appears to be mild and self-limited. Virologic rebound was more common in patients taking nirmtarelvir/ritonavir compared with untreated patients, but was also reported in patients taking molnupiravir.[683]

» Nirmatrelvir/ritonavir 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. Patients already on ritonavir-containing regimen for HIV or hepatitis C virus infection do not need to adjust the dose of their current antiviral regimen, and the dose of nirmatrelvir/ritonavir is unchanged for these patients (unless a dose adjustment is required based on the patient's renal function). Recommendations for managing drug-drug interactions may differ for patients on extended courses of nirmatrelvir/ritonavir. [IDSA: management of drug interactions with nirmatrelvir/ritonavir] (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/management-of-drug-interactions-with-nirmatrelvirritonavir-paxlovid)

adjunct **monoclonal antibody**

Treatment recommended for SOME patients in selected patient group

» Consider a monoclonal antibody in patients who are at high risk of clinical progression. Guideline recommendations vary.

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» The World Health Organization (WHO) strongly recommends against the use of sotrovimab and casirivimab/imdevimab for patients with nonsevere disease, as there is evidence of a reduction in effectiveness against currently circulating variants of SARS-CoV-2 and their subvariants. The agency makes no recommendations for other monoclonal antibodies.[406] [679] [680]

» In the UK, the National Institute for Health and Care Excellence (NICE) recommends offering sotrovimab as an option for treating patients ≥12 years of age and ≥40 kg body weight who do not need supplemental oxygen, who have an increased risk for progression to severe disease, and for whom nirmatrelvir/ritonavir is contraindicated or unsuitable.[405] [681] Tixagevimab/cilgavimab is not recommended.[701]

» In the US, the Infectious Diseases Society of America (IDSA) does not currently recommend the use of monoclonal antibodies for the treatment of COVID-19.[401]

» Choice of monoclonal antibody depends on availability, as well as clinical and contextual factors including information about efficacy with different SARS-CoV-2 variants and subvariants. [405] [406] Options may include bebtelovimab, tixagevimab/cilgavimab, casirivimab/imdevimab, sotrovimab, bamlanivimab/etesevimab, and regdanvimab, depending on your location. Check your local guidance for information about whether a particular monoclonal antibody is effective against current circulating SARS-CoV-2 variants and subvariants. 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.

» 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. Casirivimab/imdevimab decreases the risk of infection and development of clinical symptoms (high-certainty evidence). Bamlanivimab decreases the risk of infection (moderate-certainty evidence). These findings only apply to unvaccinated people, and are only applicable to variants prevailing during the study.[702] A systematic review and meta-analysis of 27 randomized controlled trials found that

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monoclonal antibodies had limited effects on most of the outcomes in nonhospitalized patients with the certainty of evidence ranging from very low to moderate for most outcomes. Monoclonal antibodies reduced hospitalization, but there were no effects on mortality.[703]

» Monoclonal antibodies are generally administered by intravenous infusion. Outpatient administration in specialized clinics is required, which may limit their feasibility.[406] Treatment should be started as soon as possible and within 7 days of symptom onset.[405] [406]

» 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.

severe disease

1st **hospital admission**

» Most patients with severe disease require hospital admission.[670] Admit patients with suspected or confirmed severe disease to an appropriate healthcare facility under the guidance of a specialist team as these patients are at risk of rapid clinical deterioration. For disease severity definitions, see Criteria .

» Implement local infection prevention and control procedures.

» 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.[405] [Clinical Frailty Scale] (https://www.dal.ca/sites/gmr/our-tools/clinical-frailty-scale.html) 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.[405] Evidence for the use of the CFS in COVID-19 is evolving despite limitations in the reporting on its application in practice.[709] Patients with a score between 4 and 9 had significantly increased mortality compared with those with a score of 1-3 in one systematic review and meta-analysis.[710] Each 1-point increase in score was associated with a 12% increase in mortality.[711] However, another systematic review and meta-analysis found that there was

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no difference in short-term mortality between frail and nonfrail patients.[712] A more nuanced understanding of frailty and outcomes is needed, and caution is required in placing too much emphasis on the influence of frailty on the prognosis of older people.[713]

» Guidance on when to stop isolation varies widely across locations. The World Health Organization (WHO) recommends 10 days of isolation for symptomatic patients, and 5 days of isolation for asymptomatic patients (based on very low-certainty evidence). Rapid antigen testing may be used to reduce the period of isolation.[444] This guidance varies and you should consult guidance from your local public health authority for more information.

adjunct **oxygen therapy**

Treatment recommended for SOME 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 hypoxemia.[444]

» Target SpO_2 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 SpO_2 >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.[444] Some guidelines recommend that SpO_2 should be maintained no higher than 96%.[715]

» Some centers may recommend different 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 in severely ill patients who require supplemental oxygen.[444] Awake prone positioning reduced the risk of endotracheal intubation compared with usual care. However, it did not significantly reduce mortality, ventilator-free days, length of stay in the intensive care unit or hospital, or escalation of oxygen modality. Adverse events were uncommon.[716]

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» Monitor patients closely for signs of progressive acute hypoxemic respiratory failure.[715]

» The World Health Organization (WHO) recommends high-flow oxygen (HFNO), continuous positive airway pressure (CPAP), or noninvasive ventilation (helmet or face mask interface) in hospitalized patients with severe disease and acute hypoxemic respiratory failure not needing emergent intubation, rather than standard oxygen therapy.[444] Choice depends on factors such as availability of devices and the supply of oxygen, personal comfort and experience, and patient-specific considerations (e.g., claustrophobia with CPAP or noninvasive ventilation masks, nasal discomfort with HFNO). Helmet bilevel positive airway pressure (BiPAP) was associated with a significantly lower intubation risk compared with HFNO and standard oxygen therapy in patients with moderate to severe disease in one meta-analysis of randomized controlled trials. Helmet BiPAP was also associated with a shorter stay in the intensive care unit compared with standard oxygen therapy. No significant differences in mortality were identified between helmet BiPAP, HFNO, standard oxygen therapy, and CPAP.[717]

plus **symptom management and supportive care**

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.

» Fluids and electrolytes: use cautious fluid management according to local guidelines. Correct any electrolyte or metabolic abnormalities, such as hyperglycemia or metabolic acidosis, according to local guidelines.[718]

» Breathlessness and cough: 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.[405] For the management of cough, advise patients to avoid lying on their back as this makes coughing ineffective, and follow your local guidelines for treating acute cough.[405]

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» Anxiety, delirium, and agitation: identify and treat any underlying or reversible causes.[405] Nonpharmacologic interventions are the mainstay for the management of delirium when possible, and prevention is key.[719]

» 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.[720]

plus **venous thromboembolism (VTE) 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 patient's risk of bleeding as soon as possible after admission, or by the time of the first attending physician review, using a suitable risk assessment tool.[405]

» If the patient is already on anticoagulation for another underlying condition, continue the current treatment dose of the anticoagulant, unless contraindicated or there is a change in clinical circumstances (e.g., bleeding develops or risk of bleeding increases).[405][704] 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.[405] A systematic review and meta-analysis found that the use of oral anticoagulation prior to hospital admission was not associated with a reduced risk of intensive care unit admission and mortality. However, the review acknowledged that further trials are needed.[721]

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» Start VTE prophylaxis in all hospitalized patients, provided that there are no contraindications.[405][704] [722] Start as soon as possible (within 14 hours of admission).[405] A Cochrane review found that anticoagulants may reduce all-cause mortality compared with no anticoagulants, but the evidence is very uncertain.[723] 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.[724]

» Low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options.[405] [704] [722] Low molecular weight heparin is preferred over unfractionated heparin and fondaparinux, unless contraindicated. [405] However, choice of anticoagulant may also depend on local guidelines. There is no high-certainty evidence comparing types of anticoagulants, but low molecular weight heparin and unfractionated heparin have been used in most studies.[725] A meta-analysis found that low molecular weight heparin was associated with decreased intensive care unit admission, mechanical ventilation, hospital stay, and mortality compared with unfractionated heparin in hospitalized patients, and there was no difference in the incidence of bleeding.[726] There is limited evidence that direct oral anticoagulants (factor Xa inhibitors) are more effective than low molecular weight heparin in preventing VTE in hospitalized patients who are not acutely ill. However, guidelines do not recommend these agents, and further randomized controlled trials are needed.[727] Consult a specialist for guidance on the choice of anticoagulant in special patient populations (e.g., children, pregnant and breastfeeding women, hepatic or renal impairment, active cancer).

» Anticoagulation dose recommendations vary, and you should consult your local guidelines. The World Health Organization (WHO) conditionally recommends prophylaxis doses of heparin (unfractionated heparin or low molecular weight heparin) instead of intermediate or therapeutic doses for severe disease, except for patients with an established indication for therapeutic anticoagulation.[406]

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» In the UK, the National Institute for Health and Care Excellence (NICE) recommends prophylaxis doses of low molecular weight heparin. However it also makes a conditional recommendation to consider treatment doses of low molecular weight heparin in those who may benefit. 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.[405]

» In the US, the American Society of Hematology (ASH) suggests using therapeutic-intensity anticoagulation over prophylactic-intensity anticoagulation, and prophylactic-intensity anticoagulation over intermediate-intensity anticoagulation, in patients with COVID-19-related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation. However, an individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. Lower-intensity anticoagulation may be preferred for patients at low thrombotic risk and high bleeding risk. These suggestions are based on very uncertain evidence.[725] The Anticoagulation Forum recommends therapeutic-intensity anticoagulation for noncritically ill patients who are not high risk for bleeding.[704] Prophylactic-dose anticoagulation is recommended by some US guidelines.[722]

» 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).[723]

» Consult a specialist for guidance on the dose of anticoagulant in special patient populations (e.g., children, pregnant and breastfeeding women, hepatic or renal impairment, active

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cancer). Dose adjustments may be required in patients with extremes of body weight or renal impairment.[405]

» Anticoagulation is generally continued until hospital discharge. Routine post-discharge VTE prophylaxis is generally not recommended, except in certain high-risk patients or if another indication for VTE prophylaxis exists.[704] [722] [725] However, in the UK, NICE recommends treatment for a minimum of 7 days, including after discharge, if standard prophylaxis doses of heparin are used.[405] If therapeutic doses of heparin are used, the recommended treatment duration is 14 days or until hospital discharge, whichever is sooner.[405] A systematic review and meta-analysis found that extended thromboprophylaxis (with either a direct oral anticoagulant or low molecular weight heparin at prophylaxis doses) administered for <35 days was significantly associated with a reduced risk of thrombosis and all-cause mortality in patients post-discharge who were at high risk of thromboembolism, without increasing the risk of major bleeding.[728]

» Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways, according to local guidelines, if clinically suspected. See Complications .

» If the patient's clinical condition changes, assess the risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.[405] Monitoring of clinical parameters during thromboprophylaxis depends on the anticoagulant and dose used. Consult your local guidelines for more information.

adjunct **antimicrobials**

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.[405] 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.

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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.[405] Antibiotics are not recommended for patients with severe disease if there is a low clinical suspicion of concurrent bacterial infection.[444] 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.[729]

» 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.[405] 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.[405]

» Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local guidelines.

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 sodium succinate: children: consult specialist for guidance on dose; adults: 50 mg 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

OR

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» methylprednisolone: children: consult specialist for guidance on dose; adults: 32 mg/day orally/intravenously given in 2-4 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 severe disease. This recommendation is based on moderate-quality evidence that suggests 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.[406] [679] [680]

» [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 (NICE) 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.[405]

» In the US, the Infectious Diseases Society of America (IDSA) recommends dexamethasone (or an alternative corticosteroid if dexamethasone is not available) for 10 days or until hospital discharge in hospitalized patients with severe disease.[401]

» Evidence supports the use of corticosteroids in hospitalized patients. A Cochrane review found that systemic corticosteroids probably slightly reduce all-cause mortality up to 30 days in hospitalized patients with symptomatic disease (moderate-certainty evidence), although the evidence is very uncertain about the effect on all-cause mortality up to 120 days. Evidence related to the most effective type, dose, or timing of corticosteroid is uncertain.[730] A living

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systematic review and network meta-analysis found that corticosteroids probably reduce mortality compared with standard care.[731] [732] Evidence suggests that higher doses may be superior to lower doses in reducing mortality in patients with severe or critical disease.[733] However, the RECOVERY trial found that higher-dose corticosteroids significantly increased the risk of death compared with usual care (which included low-dose corticosteroids) in hospitalized patients who required either no oxygen or simple oxygen only.[734] Evidence also suggests that shorter treatment courses may optimize the mortality benefit in hospitalized patients. An optimal duration of treatment was <7 days in one meta-analysis, with no additional survival benefit reported with ≥7 days of treatment.[735]

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

adjunct **antiviral**

Treatment recommended for SOME patients in selected patient group

Primary options

» remdesivir: neonates <28 days of age and ≥1.5 kg body weight: 2.5 mg/kg intravenously as a loading dose on day 1, followed by 1.25 mg/kg every 24 hours for 4-9 days; children ≥28 days of age and 1.5 to <3 kg body weight: 2.5 mg/kg intravenously as a loading dose on day 1, followed by 1.25 mg/kg every 24 hours for 4-9 days; children ≥28 days of age and 3 to <40 kg body weight: 5 mg/kg intravenously as a loading dose on day 1, followed by 2.5 mg/kg every 24 hours for 4-9 days; children ≥40 kg body weight and adults: 200 mg intravenously as a loading dose on day 1, followed by 100 mg every 24 hours for 4-9 days
Licensing and guideline recommendations for use in children vary; check your local guidelines or drug information source for more information. Only the lyophilized powder formulation is recommended in pediatric patients <40 kg body weight.

No dose adjustment is required in patients with any degree of hepatic or renal impairment (including patients on dialysis).

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» Consider the antiviral agent remdesivir. Guideline recommendations vary.

» The World Health Organization (WHO) conditionally recommends the intravenous antiviral remdesivir in adults with severe disease. This recommendation is based on low-certainty evidence that suggests remdesivir possibly reduces mortality, and moderate-certainty evidence that suggests it probably reduces the need for mechanical ventilation. Moderate-certainty evidence suggests that remdesivir probably has little or no impact on time to symptom improvement. There is insufficient evidence to make a recommendation around use in children.[406] [679] [680]

» [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 (NICE) recommends remdesivir as an option in hospitals in adults at high risk of serious illness, and children (ages 4 weeks to 17 years and weight ≥3 kg) who have pneumonia and need supplemental oxygen or who weigh ≥40 kg and have a high risk of serious illness.[405] [701]

» In the US, the Infectious Diseases Society of America (IDSA) recommends remdesivir for 5 days in patients who require supplemental oxygen.[401]

» Remdesivir should be administered as soon as possible after onset of symptoms. The recommended treatment course for this indication is 5 to 10 days or until hospital discharge, whichever comes first.[401] [405] [406] 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. There may be no benefit in completing the full course of remdesivir if the patient progresses.[405]

» Despite guidelines recommending the use of remdesivir in patients with severe disease, evidence for its use is conflicting. A Cochrane review found that remdesivir probably has little or no effect on all-cause mortality (up to 150 days) in hospitalized patients with moderate to severe disease compared with placebo or usual care (moderate-certainty evidence). Remdesivir probably increases the chance of clinical improvement up to day 28 slightly, and decreases the risk of clinical worsening within

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28 days (moderate-certainty evidence).[736] One systematic review of randomized controlled trials and real-world studies (including over 1.2 million participants) found that remdesivir significantly decreased all-cause mortality at 28-30 days in hospitalized patients, regardless of disease severity, SARS-CoV-2 variant, or vaccination era.[737] A 1-year follow-up of hospitalized patients in a randomized controlled trial found no long-term benefits (quality-of-life or symptom outcomes) for remdesivir compared with standard of care.[738]

» Remdesivir is associated with hepatotoxicity and hypersensitivity reactions. 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. Acute kidney injury has also 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.[406]

OR

» sarilumab: 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.[406]

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

» The World Health Organization (WHO) strongly recommends a single dose of an IL-6 inhibitor (tocilizumab or sarilumab) in adults with severe disease. IL-6 inhibitors may be administered in combination with corticosteroids and Janus kinase inhibitors, and should be initiated at the same time as systemic corticosteroids. 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.[406] [679] [680]

» [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 (NICE) recommends a single dose of tocilizumab in hospitalized adults who are having systemic corticosteroids and need supplemental oxygen.[405] [681]

» In the US, the Infectious Diseases Society of America (IDSA) recommends a single dose of tocilizumab (or sarilumab if tocilizumab is not available) in hospitalized patients with progressive severe disease who have elevated markers of systemic inflammation in addition to standard care (i.e., corticosteroids).[401]

» Evidence supports the use of IL-6 inhibitors. A Cochrane review found that tocilizumab reduced all-cause mortality at day 28 (high-certainty evidence) compared with standard care alone or placebo. The evidence suggests uncertainty around the effect of tocilizumab on mortality after day 60. Evidence for an effect on these outcomes for sarilumab is very uncertain. Tocilizumab and sarilumab probably result in little or no increase in clinical improvement at day 28 (i.e., hospital discharge or improvement measured by trialist-defined scales) (moderate-certainty evidence). The

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evidence for clinical improvement after day 60 is very uncertain for both drugs.[740] A living systematic review and network meta-analysis found that IL-6 inhibitors (with corticosteroids) probably reduce mortality (moderate-certainty evidence), are likely to reduce the need for mechanical ventilation (moderate-certainty evidence), and may reduce the duration of hospitalization (moderate-certainty evidence) compared with standard care.[731] [732] IL-6 inhibitors may not be beneficial when used alone (without corticosteroids).[741]

» 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.[406]

adjunct **Janus kinase (JAK) inhibitor**

Treatment recommended for SOME patients in selected patient group

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 (WHO) strongly recommends an oral JAK inhibitor (baricitinib) for 14 days or until hospital discharge (whichever is first) in adults with severe disease. Baricitinib may be administered in combination with corticosteroids and IL-6 inhibitors, and should be initiated at the same time as systemic corticosteroids. This recommendation is based on high-certainty evidence that baricitinib reduces mortality, and moderate-certainty

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evidence that baricitinib probably reduces the duration of mechanical ventilation and the length of hospital stay. The applicability of this recommendation to children is currently uncertain.[406] [679] [680]

» [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 (NICE) 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. It may also be considered in children ≥2 years of age provided they meet the same criteria.[405]

» In the US, the Infectious Diseases Society of America (IDSA) recommends baricitinib in hospitalized patients with severe disease, in addition to corticosteroid therapy. It may also be used in patients who cannot receive a corticosteroid due to a contraindication (in combination with remdesivir).[401]

» Other drugs in this class include tofacitinib and ruxolitinib. The WHO recommends against using other drugs in this class 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.[406] [679] [680]

» Evidence supports the use of JAK inhibitors. A Cochrane review found that JAK inhibitors probably reduced all-cause mortality up to day 28 (moderate-certainty evidence) and up to day 60 (high-certainty evidence). They probably make little or no difference in improvement in clinical status or the rate of adverse events (moderate-certainty evidence). Baricitinib was the most often evaluated JAK inhibitor.[742] A living systematic review and network meta-analysis found that JAK inhibitors probably reduce mortality (high-certainty evidence), reduce the duration of mechanical ventilation (high-certainty evidence), and reduce length of hospital stay (high-certainty evidence) compared with standard care.[731] [732]

» Patients are at increased risk of infection including active tuberculosis, invasive fungal infections, and opportunistic

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pathogens.[406] 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.[406] 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.[406] Other serious adverse effects include venous thrombosis and severe infections.

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.[405]

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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 **palliative care**

Treatment recommended for SOME patients in selected patient group

» Palliative care interventions should be integrated with curative treatment. Basic palliative care is recommended in all patients, as appropriate.[444] Follow local palliative care guidelines.

» There is a lack of data on palliative care in patients with COVID-19. A Cochrane review found very low-certainty evidence for the efficacy of pharmacologic interventions for palliative symptom relief, and no evidence on the safety of pharmacologic interventions or safety and efficacy of nonpharmacologic interventions for palliative symptom control. More evidence is needed to guide end-of-life management.[790] 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.[743]

critical disease

1st **intensive/critical care unit admission**

» 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. For disease severity definitions, see Criteria .

» 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

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decisions to refuse treatment with patients who have preexisting advanced comorbidities.[405]

» Implement local infection prevention and control procedures.

» Guidance on when to stop isolation varies widely across locations. The World Health Organization (WHO) recommends 10 days of isolation for symptomatic patients, and 5 days of isolation for asymptomatic patients (based on very low-certainty evidence). Rapid antigen testing may be used to reduce the period of isolation.[444] This guidance varies and you should consult guidance from your local public health authority for more information.

plus **symptom management and supportive care**

Treatment recommended for ALL patients in selected patient group

» Consider fluid and electrolyte management, antimicrobial treatment, and symptom management as appropriate. See Severe COVID-19 for more detailed information.

» Implement standard interventions to prevent complications associated with critical illness.[444] The management of sepsis and septic shock in patients with COVID-19 is beyond the scope of this topic. See Complications .

» Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local guidelines.

plus **venous thromboembolism (VTE) 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

» heparin: consult specialist for guidance on dose

OR

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» fondaparinux: consult specialist for guidance on dose

» If not already started, start VTE prophylaxis in all hospitalized patients, provided there are no contraindications.[405][704] [722] Choice of anticoagulant and anticoagulation dose recommendations vary, and you should consult your local guidelines.

» The World Health Organization (WHO) conditionally recommends prophylaxis doses of heparin (unfractionated heparin or low molecular weight heparin) instead of intermediate or therapeutic doses for critical disease, except for patients with an established indication for therapeutic anticoagulation.[406]

» In the UK, the National Institute for Health and Care Excellence (NICE) recommends a prophylactic dose of a low molecular weight heparin to young people and adults who need high-flow nasal oxygen (HFNO), continuous positive airway pressure (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.[405]

» In the US, the American Society of Hematology (ASH) suggests using prophylactic-intensity anticoagulation over intermediate- or therapeutic-intensity anticoagulation for patients with COVID-19-related critical illness who do not have suspected or confirmed VTE or another indication for anticoagulation. An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. Higher-intensity anticoagulation may be preferred for patients at high thrombotic risk and low bleeding risk. Low molecular weight heparin and unfractionated heparin have been used in most studies.[725] Other US guidelines also support the use of prophylactic-dose thromboprophylaxis for patients who are critically ill.[704] [722]

» See Severe COVID-19 for more detailed information on VTE prophylaxis. Recommendations for patients with critical disease may differ from those for severe disease and you should consult your local guidelines.

» Evidence for VTE prophylaxis is limited in patients with critical disease. A systematic

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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.[787] Another smaller systematic review and meta-analysis found no difference between escalated doses and standard prophylaxis dosing in terms of impact on mortality in critically ill patients. However, there was a reduced risk of pulmonary embolism in the escalated dose group.[788] Other meta-analyses have confirmed the lack of mortality benefit in patients with critical disease.[789]

adjunct **high-flow nasal oxygen (HFNO) or noninvasive ventilation**

Treatment recommended for SOME patients in selected patient group

» The World Health Organization (WHO) recommends HFNO, continuous positive airway pressure (CPAP), or noninvasive ventilation (helmet or face mask interface) in hospitalized patients with severe or critical disease and acute hypoxemic respiratory failure not needing emergent intubation, rather than standard oxygen therapy. Choice depends on factors such as availability of devices and the supply of oxygen, personal comfort and experience, and patient-specific considerations (e.g., claustrophobia with CPAP or noninvasive ventilation masks, nasal discomfort with HFNO).[444]

» In the UK, the National Institute for Health and Care Excellence (NICE) 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

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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.[405]

» Airborne precautions may be recommended for these interventions due to uncertainty about the potential for aerosolization. Consult your local guidelines. However, CPAP and HFNO do not appear to be associated with significant additional air or surface viral contamination compared with supplemental oxygen.[758] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[759] A systematic review and meta-analysis found no association between HFNO and noninvasive ventilation and aerosol generation-increased airborne pathogen detection.[760]

» Consider awake prone positioning in severely ill patients who require HFNO or noninvasive ventilation.[444] In the UK, NICE recommends considering awake prone positioning for hospitalized patients who are not intubated and have higher oxygen needs.[405] Awake prone positioning reduced the risk of endotracheal intubation compared with usual care. However, it did not significantly reduce mortality, ventilator-free days, length of stay in the intensive care unit or hospital, or escalation of oxygen modality. Adverse events were uncommon.[716]

» Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions, they may require urgent endotracheal intubation.[715]

» Limited evidence suggests that noninvasive ventilation reduces the need for intubation, improves resource utilization, may be associated with better outcomes, and is safe.[748] There is no certain evidence that noninvasive respiratory support increases or decreases mortality in patients with COVID-19 acute respiratory failure.[747] 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

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HFNO.[749] 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.[751] [752] HFNO may reduce intubation rate and 28-day intensive care unit mortality, and may improve 28-day ventilator-free days compared with conventional oxygen therapy in patients with acute respiratory failure. However, large-scale randomized controlled trials are necessary.[753] 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.[754] The HELMET-COVID trial (a multicenter randomized clinical trial) found that helmet noninvasive ventilation did not significantly reduce 28-day mortality compared with usual respiratory support (alternate use of mask noninvasive ventilation, HFNO, or standard oxygen according to clinical response) among patients with acute hypoxemic respiratory failure. However, there were several important limitations to the study, and interpretation of the findings is limited by imprecision in the effect size estimate.[755] The SOHO-COVID trial (a randomized clinical trial) found that HFNO did not significantly reduce 28-day mortality compared with standard oxygen therapy among patients with respiratory failure.[756] However, 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.[757]

adjunct **invasive mechanical ventilation**

Treatment recommended for SOME patients in selected patient group

» Consider endotracheal intubation and mechanical ventilation in patients with acute respiratory distress syndrome (ARDS) who are acutely deteriorating despite advanced oxygen/noninvasive ventilatory support measures.[444] [715]

» 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

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based on random-effect pooled estimates. Outcomes appear to have improved as the pandemic has progressed.[761] However, results have not been consistent.[762] Early intubation may be associated with lower all-cause mortality compared with patients undergoing late intubation. However, again, results have not been consistent.[763] [764]

» 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 suggested 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.[444] [715]

» Although some patients with COVID-19 pneumonia meet the criteria for ARDS, there has been some discussion about whether COVID-19 pneumonia is its own specific disease with atypical phenotypes. Anecdotal evidence from early in the pandemic suggested that the main characteristic of the atypical presentation was the dissociation between well-preserved lung mechanics and the severity of hypoxemia.[765] [766] [767] [768] [769] [770] However, this hypothesis was criticized.[771] [772] A systematic review and meta-analysis published in late 2022 found no evidence for distinct respiratory system static compliance-based clinical phenotypes in patients with COVID-19-related ARDS.[773]

» 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.[774] However, some clinicians have warned that protocol-driven ventilator use may cause 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.[765] Therefore, PEEP should always be carefully titrated.[775]

» 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

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position. Caution is required in children.[444] [715] Longer durations may be feasible in some patients.[776] Lung recruitment maneuvers are suggested, but staircase recruitment maneuvers are not recommended.[715] A systematic review and meta-analysis found that there was no significant difference in mortality between prone and supine positioning, and that hospital stay was significantly higher in the prone position group. There was no difference between the two groups in terms of length of stay in the intensive care unit and days of mechanical ventilation.[777]

adjunct **inhaled pulmonary vasodilator**

Treatment recommended for SOME patients in selected patient group

» Consider a trial of an inhaled pulmonary vasodilator in adults and children who have severe acute respiratory distress syndrome and refractory hypoxemia despite optimizing ventilation. Taper off if there is no rapid improvement in oxygenation.[715]

» Evidence is emerging. A systematic review and meta-analysis found that inhaled pulmonary vasodilators may improve oxygenation, but showed no mortality benefit, compared with standard therapy.[778]

adjunct **extracorporeal membrane oxygenation (ECMO)**

Treatment recommended for SOME patients in selected patient group

» Consider ECMO according to availability and expertise if other methods fail.[715]

» Evidence to support the use of ECMO is limited.

» A registry-based cohort study found that ECMO was associated with a 7.1% reduction in mortality in selected adults (i.e., PaO_2/FiO_2 <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 PaO_2/FiO_2 <80 mmHg or with driving pressures >15 cm H_2O during the first 10 days of mechanical ventilation.[779]

» Pooled mortality rates in adults receiving ECMO ranged from 39% to 49%.[780] [781] The mortality rate in children was 26.6%.[782] Factors associated with an increased risk of mortality included older age, male

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sex, chronic lung disease, longer duration of symptoms, longer duration of invasive mechanical ventilation, higher driving pressure, and higher partial pressure of arterial carbon dioxide.[783]

» There is a high risk of thrombotic and neurologic complications (e.g., circuit thrombosis, major bleeding, intracranial hemorrhage, ischemic stroke, and hypoxic ischemic brain injury) in patients on ECMO.[784] [785] [786]

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 sodium succinate: children: consult specialist for guidance on dose; adults: 50 mg 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

OR

» methylprednisolone: children: consult specialist for guidance on dose; adults: 32 mg/day orally/intravenously given in 2-4 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 moderate-quality evidence that suggests 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

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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.[406] [679] [680]

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» In the UK, the National Institute for Health and Care Excellence (NICE) 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.[405]

» In the US, the Infectious Diseases Society of America (IDSA) recommends dexamethasone (or an alternative corticosteroid if dexamethasone is not available) for 10 days or until hospital discharge in critically ill patients.[401]

» Evidence supports the use of corticosteroids in hospitalized patients. A Cochrane review found that systemic corticosteroids probably slightly reduce all-cause mortality up to 30 days in hospitalized patients with symptomatic disease, although the evidence is very uncertain about the effect on all-cause mortality up to 120 days. Evidence related to the most effective type, dose, or timing of corticosteroid is uncertain.[730] Evidence suggests that higher doses may be superior to lower doses in reducing mortality in patients with severe or critical disease.[733] However, the RECOVERY trial continues to assess higher doses in hospitalized patients who require noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[734] Evidence also suggests that shorter treatment courses may optimize the mortality benefit in hospitalized patients. An optimal duration of treatment was <7 days in one meta-analysis, with no additional survival benefit reported with ≥7 days of treatment.[735]

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

Acute

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.[406]

OR

» sarilumab: 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.[406]

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

» The World Health Organization (WHO) strongly recommends a single dose of an IL-6 inhibitor (tocilizumab or sarilumab) in adults with critical disease. IL-6 inhibitors may be administered in combination with corticosteroids and Janus kinase inhibitors, and should be initiated at the same time as systemic corticosteroids. 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.[406] [679] [680]

» [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 (NICE) recommends a single dose of tocilizumab in hospitalized adults who are having systemic corticosteroids and need supplemental oxygen or mechanical ventilation.[405] [681]

Acute

» In the US, the Infectious Diseases Society of America (IDSA) recommends a single dose of tocilizumab (or sarilumab if tocilizumab is not available) in critically ill patients who have elevated markers of systemic inflammation in addition to standard care (i.e., corticosteroids). [401]

» Evidence supports the use of IL-6 inhibitors. A Cochrane review found that tocilizumab reduced all-cause mortality at day 28 (high-certainty evidence) compared with standard care alone or placebo. The evidence suggests uncertainty around the effect of tocilizumab on mortality after day 60. Evidence for an effect on these outcomes for sarilumab is very uncertain. Tocilizumab and sarilumab probably result in little or no increase in clinical improvement at day 28 (i.e., hospital discharge or improvement measured by trialist-defined scales) (moderate-certainty evidence). The evidence for clinical improvement after day 60 is very uncertain for both drugs.[740] A living systematic review and network meta-analysis found that IL-6 inhibitors (with corticosteroids) probably reduce mortality (moderate-certainty evidence), are likely to reduce the need for mechanical ventilation (moderate-certainty evidence), and may reduce the duration of hospitalization (moderate-certainty evidence) compared with standard care.[731] [732] IL-6 inhibitors may not be beneficial when used alone (without corticosteroids).[741]

» 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.[406]

adjunct **Janus kinase (JAK) inhibitor**

Treatment recommended for SOME patients in selected patient group

Primary options

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

Secondary options

Acute

» 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 (WHO) strongly recommends an oral JAK inhibitor (baricitinib) for 14 days or until hospital discharge (whichever is first) in adults with critical disease. Baricitinib may be administered in combination with corticosteroids and IL-6 inhibitors, and should be initiated at the same time as systemic corticosteroids. This recommendation is based on high-certainty evidence that baricitinib reduces mortality, and moderate-certainty evidence that baricitinib probably reduces the duration of mechanical ventilation and the length of hospital stay. The applicability of this recommendation to children is currently uncertain.[406] [679] [680]

» [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 (NICE) 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. It may also be considered in children ≥2 years of age provided they meet the same criteria.[405]

» In the US, the Infectious Diseases Society of America (IDSA) recommends baricitinib in critically ill patients receiving HFNO or noninvasive ventilation (and patients receiving invasive ventilation or ECMO when IL-6 inhibitors are not available), in addition to corticosteroid therapy.[401]

» Other drugs in this class include tofacitinib and ruxolitinib. The WHO recommends against using other drugs in this class 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.[406] [679] [680]

Acute

» Evidence supports the use of JAK inhibitors. A Cochrane review found that JAK inhibitors probably reduced all-cause mortality up to day 28 (moderate-certainty evidence) and up to day 60 (high-certainty evidence). They probably make little or no difference in improvement in clinical status or the rate of adverse events (moderate-certainty evidence). Baricitinib was the most often evaluated JAK inhibitor.[742] A living systematic review and network meta-analysis found that JAK inhibitors probably reduce mortality (high-certainty evidence), reduce the duration of mechanical ventilation (high-certainty evidence), and reduce length of hospital stay (high-certainty evidence) compared with standard care.[731] [732]

» Patients are at increased risk of infection including active tuberculosis, invasive fungal infections, and opportunistic pathogens.[406] 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.[406] 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.[406] Other serious adverse effects include venous thrombosis and severe infections.

adjunct **palliative care**

Acute

Treatment recommended for SOME patients in selected patient group

» Palliative care interventions should be integrated with curative treatment. Basic palliative care is recommended in all patients, as appropriate.[444] Follow local palliative care guidelines.

» There is 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.[743]

Emerging

Vilobelimab

Vilobelimab is a first-in-class, intravenous anti-C5a monoclonal antibody. C5a plays a role in severe lung injury. A phase 3, double-blind, randomized placebo-controlled trial found that vilobelimab, in addition to standard of care, reduced mortality at 28 and 60 days in critically ill patients on invasive mechanical ventilation (absolute risk reduction of 11%) compared with placebo.[798] The Food and Drug Administration (FDA) has issued an emergency-use authorization for the use of vilobelimab for the treatment of hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). The European Medicines Agency (EMA) has also authorized the use of vilobelimab for this indication. Guidelines recommend vilobelimab in critically ill hospitalized adults who require mechanical ventilation or ECMO, only in the context of a clinical trial. Additional data are needed to assess the safety and efficacy of vilobelimab when given to patients receiving immunomodulators for the treatment of COVID-19, and to patients who are immunocompromised. Further research is also needed on efficacy when given after 48 hours of intubation.[401]

Anakinra

Anakinra is an interleukin (IL)-1 inhibitor that is approved in Europe for adults with COVID-19 pneumonia who require low- or high-flow nasal oxygen (HFNO) 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. It is authorized under an emergency-use authorization in the US for the same indication. Guidelines suggest against the routine use of anakinra for the treatment of COVID-19.[401] Systematic reviews and meta-analyses have found that anakinra may reduce mortality and the need for invasive mechanical ventilation in hospitalized patients, particularly those with C-reactive protein levels >100 mg/L, compared with standard care alone.[799] [800] [801] However, a Cochrane review did not find evidence for an important beneficial clinical effect of IL-1 inhibitors, and the evidence is uncertain for several outcomes. Anakinra probably results in little or no improvement in symptoms at 28 days after treatment (moderate-certainty evidence). It is uncertain whether anakinra makes a difference to the number of deaths at 28 days after treatment (low-certainty evidence).[802]

Colchicine

Colchicine is an anti-inflammatory agent that downregulates multiple pro-inflammatory pathways. Guidelines recommend against the use of colchicine for the treatment of COVID-19.[401][405] [406] 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.[803]

Convalescent plasma

High-titer convalescent plasma is a blood product that contains high titers of antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from patients who have recovered. Guidelines recommend against the use of convalescent plasma for the treatment of hospitalized patients with COVID-19, except in the context of a clinical trial.[401][406] Guideline recommendations in patients with nonsevere disease are conflicting. Some guidelines recommend it in select patients (e.g., outpatients who are at high risk for progression to severe disease who have no other treatment options).[401] [804] Other guidelines recommend against its use in these patients.[406] A Cochrane review found that convalescent plasma does not reduce all-cause 28-day mortality, and has little to no impact on measures of clinical improvement for the treatment of moderate to severe disease, compared with placebo or standard care alone (high-certainty evidence).[805] A living systematic review and network meta-analysis found that convalescent plasma may not confer any meaningful benefit in patients with any disease severity, but whether high-titer convalescent plasma confers any benefit remains uncertain.[806] 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 and hospitalization, especially in immunocompromised people, and when trials with low-titer convalescent plasma were removed from the analyses.[807] [808] [809] [810] [811] [812][813] [814]

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. A Cochrane review found that IVIG may have little to no impact on mortality and clinical improvement and worsening compared with standard therapy in patients with moderate to severe disease, but may increase adverse events. However, the evidence is uncertain and studies were conducted before the vaccine rollout and the emergence of variants of concern.[815] A living systematic review and network meta-analysis found that IVIG may not confer any meaningful benefit in patients with any disease severity.[806] However, other meta-analyses have found that IVIG may reduce mortality in patients with severe or critical disease.[816] [817]

Granulocyte-macrophage colony-stimulating factor inhibitors

Investigational granulocyte-macrophage colony-stimulating factor (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. Randomized controlled trials have shown positive results for lenzilumab, but not mavrilimumab.[818] [819] A meta-analysis found that GM-CSF inhibitors may reduce the incidence of mechanical ventilation and decrease mortality, but evidence is limited and further studies are required.[820]

Stem cell therapy

Mesenchymal stem cells are an investigational product that have been studied for their immunomodulatory properties. Systematic reviews and meta-analyses have found that mesenchymal stem cells may reduce the incidence of adverse events and mortality in patients with severe or critical disease. However, evidence is limited.[821] [822] [823]

Interferons

Interferons are a family of cytokines with antiviral properties. The WHO Solidarity trial found that interferon beta appears to have little or no effect on hospitalized patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[824] 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.[825] A randomized controlled trial found that a single dose of pegylated interferon lambda reduced the incidence of hospitalization or an emergency department visit compared with placebo, among predominantly vaccinated outpatients.[826]

Ivermectin

Ivermectin is a broad-spectrum antiparasitic agent that has shown to be effective against SARS-CoV-2 in vitro.[827] Guidelines do not recommend ivermectin for the treatment of COVID-19, except in the context of a clinical trial for severe or critical disease (in research settings only).[401][405] [406] There is insufficient evidence to be clear to what extent ivermectin is helpful or harmful. For most key outcomes, including mortality, mechanical ventilation, hospital admission, duration of hospitalization, and viral clearance, the evidence is of very low certainty.[679] [680] Data from meta-analyses are conflicting. A meta-analysis of 24 randomized controlled trials found that ivermectin provided a significant survival benefit (moderate-certainty evidence), and a likely clinical benefit in terms of improvement and deterioration (low-certainty evidence). Overall, the evidence suggested that early use may reduce morbidity and mortality.[828] Other meta-analyses also support an improvement in clinical outcomes, although the quality of evidence was very low to low.[829] [830] [831] [832][833] However, there are other meta-analyses that have found that ivermectin does not reduce all-cause mortality or result in improvement in other clinical outcomes.[834] [835] [836] [837] A Cochrane review found that ivermectin has no beneficial effect in outpatients (low- to high-certainty evidence). It also has no beneficial effect on clinical improvement or viral clearance in inpatients, but the evidence for whether it prevents death or clinical worsening in inpatients is uncertain (low-certainty evidence).[838]

Fluvoxamine

Fluvoxamine is a selective serotonin-reuptake inhibitor that has anti-inflammatory and possible antiviral effects. Guidelines recommend against the use of fluvoxamine for the treatment of COVID-19, except in the context of a clinical trial.[401][406] A Cochrane review found that fluvoxamine (in addition to standard care) may slightly reduce 28-day all-cause mortality and reduce the risk of hospital admission or mortality in patients with mild disease, compared with standard care plus placebo (low-certainty evidence).[839] A meta-analysis of randomized controlled trials, including the TOGETHER trial, 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.[840]

Sabizabulin

Sabizabulin is an investigational drug that binds to the microtubules in cells (similar to colchicine), thereby interfering with the lifecycle of the SARS-CoV-2 virus, and has antiviral and anti-inflammatory effects. The FDA voted against an emergency-use authorization for use in hospitalized patients with moderate to severe infection. However, the manufacturer plans to continue late-stage development of the drug. Interim results from a small phase 3 trial (204 patients) found that sabizabulin was associated with a reduction in mortality compared with placebo (45% versus 20%).[841]

VV116 (oral remdesivir)

An oral formulation of remdesivir, known as VV116 (a remdesivir derivative), is currently in development. Guidelines recommend against the use of VV116 for the treatment of COVID-19, except in the context of a clinical trial.[406] A phase 3 randomized controlled trial found that a 5-day course of VV116 was noninferior to nirmatrelvir/ritonavir in shortening time to sustained clinical recovery in symptomatic adults with mild to moderate disease who were at risk for progression to severe disease, with fewer safety concerns (during the Omicron period).[842] A phase 3 randomized controlled trial found that a 5-day course of VV116 significantly reduced the time to sustained clinical symptom resolution in patients with mild to moderate disease, regardless of the presence of high-risk factors for progression to severe disease or vaccination status, compared with placebo.[843]

Ensitrelvir

An investigational novel oral antiviral that works by selectively inhibiting viral 3CL protease. It is currently approved in Japan under an emergency regulatory approval, but is not approved in other countries. Ensitrelvir has demonstrated in vitro antiviral activity against the Omicron BA.4 and BA.5 subvariants.[844] A phase 2/3 randomized controlled trial found that ensitrelvir reduced the time to resolution of five typical Omicron-related symptoms (by approximately 1 day) compared with placebo in patients with mild to moderate disease treated in less than 72 hours of disease onset.[845] [846] One systematic review and meta-analysis found that ensitrelvir reduced viral load compared with placebo, but was associated with significant adverse effects (e.g., elevated triglycerides, increased bilirubin).[847] Another systematic review found that ensitrelvir was associated with a reduced risk of death and shorter hospital stays in patients with mild to moderate disease.[848] Several other phase 3 clinical studies are either ongoing or planned. The FDA has granted fast-track designation to ensitrelvir.

Olgotrelvir

An investigational oral SARS-CoV-2 main protease (Mpro) inhibitor that has a broad spectrum of antiviral activity, including against the original SARS-CoV-2 virus and the Omicron variant. Olgotrelvir avoids the concomitant use of the CYP3A4 inhibitor ritonavir, lowering the risk of drug-drug interactions compared with nirmatrelvir/ritonavir. A phase 3 trial has been completed.[849]

Simnotrelvir

An investigational oral 3-chymotrypsin-like protease inhibitor antiviral. A phase 2/3 double-blind, randomized, placebo-controlled trial found that early administration of simnotrelvir plus ritonavir significantly shortened the time to the resolution of symptoms and reduced viral load at day 5 in adults, compared with placebo.[850]

Bemnifosbuvir

An investigational oral direct-acting antiviral. Bemnifosbuvir targets SARS-CoV-2 RNA polymerase, and inhibits both RNA-dependent RNA polymerase and nucleotidyltransferase. It is currently being evaluated in the global SUNRISE-3 trial, a randomized, double-blind, placebo-controlled phase 3 trial.[851] The FDA has granted fast-track designation to bemnifosbuvir for the treatment of COVID-19.

Inhaled corticosteroids

Inhaled corticosteroids are thought to modulate the inflammatory pathways in the upper respiratory tract and circulation following infection. Guidelines do not recommend inhaled corticosteroids for the treatment of COVID-19, except in the context of a clinical trial.[401] [405] Patients who are on an inhaled corticosteroid for other indications should continue treatment.[401] 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, inhaled corticosteroids make little to no difference in all-cause 30-day mortality but may decrease duration to symptom resolution (low-certainty evidence).[852]

Aspirin

Aspirin (and other antiplatelet drugs) are not currently recommended by guidelines, and the evidence for their use is conflicting. The RECOVERY trial found that aspirin was not associated with a reduction in 28-day mortality or a reduced risk of progression to ventilation or death, and was associated with an increased risk of major bleeding events.[853] Other randomized controlled trials also demonstrate no benefit with aspirin (alone or in combination with rivaroxaban).[854] [855] However, meta-analyses have found that aspirin may reduce mortality.[856] [857] Further randomized controlled trials are required.

Antibiotics

Azithromycin and tetracyclines have been investigated for the treatment of COVID-19. Guidelines recommend against the use of these antibiotics for the treatment of COVID-19 in the absence of another indication for their use.[405] A Cochrane review found that azithromycin did not reduce 28-day all-cause mortality in hospitalized patients compared with standard 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).[858] A living systematic review and network meta-analysis found that azithromycin probably reduces time to symptom resolution compared with standard care (moderate-certainty evidence).[690] 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.[859]

Vitamins and minerals and supplements

Vitamin C, vitamin D, and zinc have shown promise in the treatment of viral respiratory tract infections.[860] [861] [862] Meta-analyses found that high-dose vitamin C reduced the risk of severe disease and mortality.[863] [864] However, these findings are inconsistent with other meta-analyses and need to be substantiated by further large-scale studies.[865] [866] A Cochrane review found there is currently insufficient evidence to determine the benefits and harms of vitamin D supplementation, and 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.[867] Meta-analyses have found that vitamin D may be associated with improved clinical outcomes, including decreased risk of intensive care admission, reduced length of hospital stay, and decreased mortality, and that there may be a potential role for vitamin D supplementation in reducing disease severity, although results are conflicting, possibly due to the inclusion of small-size randomized trials in the analysis.[868][869] [870] [871] [872] [873] [874] The UK National Institute for Health and Care Excellence (NICE) does not recommend supplementation to solely prevent or treat COVID-19, except as part of a clinical trial.[405] Meta-analyses have found that that zinc supplementation may be associated with a decreased risk of mortality.[875] [876] A systematic review and meta-analysis of randomized controlled trials found that omega-3 fatty acids may be associated with reduced mortality in hospitalized patients, although the sample size was small.[877]

Probiotics

Probiotics have been used in a variety of conditions, including respiratory infections. A systematic review and meta-analysis found that probiotics were associated with a 51% reduction in reported symptoms, with improvement noted in cough, headache, and diarrhea.[878] Probiotics may also shorten hospital stay and mortality.[879] [880] However, further research is required.

Melatonin

Melatonin has antioxidant, anti-inflammatory, immunomodulatory, and antiviral properties. Small studies have suggested an improvement in symptoms and clinical outcomes, including in-hospital mortality in patients with severe to critical disease.[881] [882][883] [884] However, further research is required.

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.[885] 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).[886]

Clinical trials

Various other treatments are in clinical trials around the world. International trials to identify treatments that may be beneficial, such as the World Health Organization's Solidarity trial, and the UK's randomized evaluation of COVID-19 therapy (RECOVERY) trial, are ongoing. [RECOVERY trial] (https://www.recoverytrial.net) [WHO: COVID-19 Solidarity therapeutics trial] (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments)

Primary prevention

Vaccines

- The World Health Organization (WHO) currently recommends vaccination based on priority groups that reflect the risk of severe disease and death.[370]
- Numerous COVID-19 vaccines are available globally. Examples may include:
  - mRNA vaccines: Comirnaty® (Pfizer/BioNTech); Spikevax® (Moderna)
  - Protein subunit vaccines: Nuvaxoid® (Novavax); Corbevax® (Biological E limited)
  - Inactivated virus vaccines: Covilo® (Sinopharm); CoronaVac® (Sinovac); VLA2001 (Valneva); BBV152 Covaxin® (Bharat Biotech)
  - Adenovirus vector vaccines: no longer available in most countries
- Next-generation mRNA vaccines (e.g., mNexspike®) that specifically encode receptor-binding and N-terminal domains of the virus, as opposed to the full-length viral spike protein, and self-amplifying mRNA vaccines (e.g., Kostaive®) have been approved in some countries.

- Vaccine availability differs between geographic locations and you should consult your local public health authority for more information on which vaccines are available in your area.
  - Monovalent or bivalent vaccines may be available. Vaccines are being adapted to better match the currently circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants and are being updated annually, similar to the influenza vaccine.
- Consult your local guidelines for information on who to vaccinate, choice of vaccine, dose schedule, and contraindications/cautions.
  - [WHO: COVID-19 vaccines technical documents] (https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials)
  - [UK Health Security Agency: COVID-19 - the green book, chapter 14a] (https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a)
  - [CDC: interim clinical considerations for use of COVID-19 vaccines in the United States] (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html)
- Administer the vaccination series according to local public health authority recommendations.
  - The schedule generally consists of a primary vaccination series (additional doses may be recommended for immunocompromised people), and booster doses in certain populations. Vaccines are included in routine immunization schedules in some countries.
- Vaccines are effective at reducing the risk of symptomatic, severe, and critical disease.
  - A Cochrane review found that most vaccines reduce (or likely reduce) the proportion of people with symptomatic disease. There is high-certainty evidence that some vaccines may reduce severe or critical disease. There is insufficient evidence to determine whether there was a reduction in mortality compared with placebo. Most studies assessed the vaccine for a short period after injection (2 months); therefore, it is unclear whether protection wanes over time. Most studies were conducted before the emergence of variants of concern.[371]
  - The 2024-2025 COVID-19 vaccine was approximately 45% effective against hospitalization in immunocompetent adults age ≥65 years compared with not receiving a 2024-2025 COVID-19 vaccine, based on data from the US. The efficacy against hospitalization in immunocompromised adults age ≥65 years was 40%.[372]
- Evidence in special patient populations is limited.
  - Pregnancy: systematic reviews and meta-analyses have found that vaccinated pregnant women are at reduced risk of infection and hospitalization compared with unvaccinated pregnant women, with no evidence of a higher risk of adverse outcomes. However, the evidence is of low certainty in some studies, the data may have limitations, and monitoring is ongoing.[373] [374] [375] [376] [377] [378] Vaccinated women had a higher risk of gestational diabetes compared with unvaccinated women in one study; however, this was based on two different populations from the same comparative cohort study, and the link needs to be explored further.[378] [379] Vaccination during pregnancy may protect the infant against infection and reduce the risk of hospitalization.[380] [381] [382][383]
  - Breastfeeding: vaccine-derived mRNA has been detected in the breast milk of women who received vaccination within 6 months of delivery. The implications of this are unknown, and further research is required.[384] [385]
  - Children and adolescents: available evidence suggests safety and efficacy are acceptable in children and adolescents. 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.[386]
- Adverse events vary and may depend on the specific vaccine. Consult the relevant prescribing information for more information.
  - Rare adverse events include: myocarditis/pericarditis; transverse myelitis; Guillain-Barre syndrome; acute disseminated encephalomyelitis; menstrual disturbances; acute peripheral facial paralysis; thromboembolic events; and immune thrombocytopenia. See Complications

. Other serious adverse events have also been reported in clinical trials, case reports, case studies, and observational studies.[387] [388] [389] [390] [391] [392] [393][394] [395] [396]
  - A secondary analysis of phase 3 randomized clinical trials of mRNA vaccines in adults found an excess risk of serious adverse events of special interest of 12.5 per 10,000 vaccinated, which suggests a higher risk than initially estimated at the time of emergency authorization.[397]
  - One self-controlled case series analysis found minimal evidence of an increased incidence of cardiac or all-cause mortality overall in the 12 weeks following vaccination (for all vaccines). However, there is evidence of a smaller increased incidence of cardiac or all-cause mortality after a second dose of an mRNA vaccine in males, and after a first dose of a non-mRNA-based vaccine among females.[398] Another self-controlled case series analysis found that vaccination was associated with an increased risk of cardiac-related mortality, especially among males.[399]
  - Vaccine adverse effects have similarities and differences to long COVID, and these syndromes should be differentiated from each other. Further research is required.[400]
- Report all suspected adverse events via your local reporting system (this is mandatory in some countries).
  - mRNA vaccines have not been authorized for use in humans previously, so there is no long-term safety data available.

Pre-exposure prophylaxis

- Pemivibart, a broadly neutralizing extended half-life monoclonal antibody with activity against SARS-CoV-2, has demonstrated in vitro neutralization against recent SARS-CoV-2 variants. It is authorized in some countries for pre-exposure prophylaxis.
  - In the US, the Infectious Diseases Society of America (IDSA) recommends pre-exposure prophylaxis with pemivibart in moderately to severely immunocompromised people ≥12 years of age who are at risk for progression to severe disease. It should only be used when the predominant regional variants are susceptible to the drug.[401]
  - Other guidelines do not currently recommend the use of pemivibart.
  - An interim analysis of the multi-cohort phase 3 CANOPY study found that pemivibart provided prophylactic efficacy against COVID-19; however, full results of the trial are yet to be published. Anaphylaxis was a rare, but important, safety risk.[402]
- Sipavibart, a broadly neutralizing extended half-life monoclonal antibody with activity against certain SARS-CoV-2 variants, is authorized in some countries for pre-exposure prophylaxis.
  - In Europe, sipavibart is authorized for the pre-exposure prophylaxis of COVID-19 in people ≥12 years of age (and ≥40 kg body weight) who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments.
  - Guidelines do not currently recommend the use of sipavibart.
  - A primary analysis of the ongoing phase 3 SUPERNOVA randomized controlled trial found that sipavibart reduced the risk of symptomatic disease due to non-Phe456Leu-containing SARS-CoV-2 variants in immunocompromised participants with an acceptable safety profile. However, Phe456Leu-containing variants are more dominant (as of November 2024), which limits the clinical utility of sipavibart at this time.[403]
- Tixagevimab/cilgavimab, a long-acting neutralizing monoclonal antibody combination with activity against SARS-CoV-2, may be authorized in some countries for pre-exposure prophylaxis.
  - However, guidelines do not currently recommend tixagevimab/cilgavimab for pre-exposure prophylaxis, as currently circulating SARS-CoV-2 subvariants are unlikely to be susceptible. [404][405] [406] [407]
  - Evidence for the use of tixagevimab/cilgavimab is limited.
  - A systematic review and meta-analysis found that tixagevimab/cilgavimab was associated with a reduction in RT-PCR positivity, symptomatic disease, severe disease, hospitalization, intensive care unit admission, need for oxygen, and mortality compared with no treatment or another

    alternative treatment. Its activity may be reduced for the Omicron BA.1 and BA.2 subvariants, but it likely maintains most of its activity against the BA.4 and BA.5 subvariants.[408]
    - Another meta-analysis found that tixagevimab/cilgavimab significantly reduced infection rates by 4.4%, hospitalization by 0.8%, and mortality rate by 0.5% in immunocompromised patients (including transplant recipients) compared with placebo. The study period included various Omicron variants.[409]
- Other monoclonal antibodies may be available for prophylaxis in some countries (e.g., amubarvimab/romlusevimab is approved for use in China and is currently being assessed for authorization in the US, casirivimab/imdevimab is authorized for use for prophylaxis in Europe).[410]
- No drugs used for prophylaxis (e.g., ivermectin, hydroxychloroquine, lopinavir/ritonavir) have provided convincing evidence for a reduction in the risk of infection. However, much of the evidence remains very low-certainty.[411] [412]
    - The WHO strongly recommends against administering hydroxychloroquine prophylaxis to people who do not have COVID-19, based on high-certainty evidence.[404]

Infection prevention and control for healthcare professionals

- Consult local infection prevention and control protocols; only basic principles from the WHO guidelines are detailed here.[413]
- 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, preferably in an isolation room, area, or single-patient room, if available. Maintain a physical distance of at least 3 feet (1 meter) between patients (increase distance where feasible).
- Implement standard precautions at all times, which include, but are not limited to:
    - Risk assessment
    - Hand hygiene
    - Respiratory hygiene and cough etiquette
    - Patient placement
    - Personal protective equipment
    - Aseptic technique
    - Environmental cleaning
    - Waste management
- Implement additional transmission-based precautions (contact, droplet, and airborne) when providing direct care for suspected or confirmed cases.
    - A respirator or medical mask should be worn along with other personal protective equipment (i.e., gown, gloves, eye protection) when providing care to 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.
    - Appropriate mask fitting for respirators and medical masks should always be ensured, as should compliance with appropriate use of personal protective equipment and other standard or transmission-based precautions.
    - Universal masking is strongly recommended in health facilities when there is a significant impact of COVID-19 on the health system.
- Implement airborne precautions when performing aerosol-generating procedures, including placing patients in an airborne infection isolation room and wearing a 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 rapid review and meta-analysis found that wearing personal protective equipment conferred significant protection against infection compared with not wearing it. High-certainty evidence indicates that using N95 masks significantly reduces the risk of infection. No effect was found for wearing gloves and gowns. There is a lack of evidence for different combinations of personal protective equipment.[414]
    - An expert panel statement informed by review-level evidence (as of May 2022) concluded that N95 respirators (or their equivalent) may be more effective than surgical masks in reducing the risk of infection in the mask wearer (low confidence) based on epidemiologic evidence (usually of low or very low certainty) from SARS-CoV-2 and other coronaviruses.[415]
    - One systematic review and meta-analysis found a protective effect for N95 respirators (particularly for medical staff), but surgical masks were not associated with a lower risk of infection.[416]
- Healthcare workers who have signs or symptoms of infection should be excluded from their activities at work that require providing in-person care to patients or other activities in the healthcare facility where they are in contact with other health and care personnel.
    - Consultation with the occupational health and safety department is recommended, and local policies should be followed regarding isolation (e.g., 5 days if asymptomatic, 10 days if symptomatic) and testing (e.g., rapid antigen testing may be used to reduce the period of isolation).
- Patients can be managed remotely by telephone or video consultations depending on local protocols.[417]
- Detailed infection prevention and control guidance is available:
    - [WHO: infection prevention and control in the context of COVID-19 - a guideline] (https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC-guideline-2023.4)
    - [CDC: infection control guidance - SARS-CoV-2] (https://www.cdc.gov/covid/hcp/infection-control/index.html)

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 feet (1 meter) away from others (recommendations on distance vary between countries), wash their hands often with soap and water (or hand sanitizer that contains at least 60% alcohol), cover coughs and sneezes, avoid crowds and poorly ventilated spaces, clean and disinfect high touch surfaces, monitor their health and self-isolate or seek medical attention if necessary, and get vaccinated.[418]
    - [WHO: advice for the public – coronavirus disease (COVID-19)] (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public)
- The WHO strongly recommends mask use in community settings in higher-risk situations regardless of the local epidemiologic situation (e.g., poorly ventilated spaces, following recent exposure to COVID-19 when sharing spaces with others, people at high risk of severe complications), and conditionally recommends a risk-based approach for mask use in community settings in other situations.[413] Public health recommendations vary between countries and you should consult your local guidance.
    - There is no high-quality or direct scientific evidence to support the widespread use of masks by healthy people in the community setting.

    - A Cochrane review, which included results of studies from during the COVID-19 pandemic, found that the pooled results of randomized controlled trials did not show a clear reduction in respiratory viral infection with the use of surgical masks. Mask use in the community setting probably makes little or no difference to the outcome of laboratory-confirmed influenza or COVID-19 compared with not wearing masks (moderate-certainty evidence). There were no clear differences between the use of N95/P2 respirators and surgical masks in healthcare workers when used in routine care to reduce the risk of respiratory viral infection, and the evidence was very uncertain.[419]
    - A living rapid review found that masks may be associated with a small reduction in risk for infection in community settings (low- to moderate-strength evidence), and surgical masks and N95 respirators may be associated with a similar infection risk in routine patient care settings.[420] [421]
    - The only randomized controlled trial to investigate the efficacy of masks in the community during the pandemic 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).[422]
    - A systematic review in children found no effect of mask wearing on infection or transmission across the majority of observational studies. There were no randomized controlled trials in children.[423]
    - 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.[424] [425]
    - Harms and disadvantages of wearing masks include headache, breathing difficulties, cognitive fatigue, 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.[413] [426] [427][428]
    - [The BMJ Clinical Review: the role of masks and respirators in preventing respiratory infections in healthcare and community settings] (https://www.bmj.com/content/388/bmj-2023-078573)
- Many countries implemented nonpharmaceutical interventions during the pandemic 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). 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.[429]
- Many countries implemented travel-control measures during the pandemic including complete or partial closure of borders, entry or exit screening, and/or quarantine of travelers. However, evidence to support the use of these measures was of low to very low certainty.[430] [431] [432]

Lifestyle modifications

- There is a lack of data on the use of lifestyle modifications and their impact on COVID-19. Further research is required.
- Lifestyle modifications (e.g., smoking cessation, weight loss, nutritious diet) may help to reduce the risk of infection, and may be a useful adjunct to other interventions.[433] [434]
- The WHO recommends that tobacco users stop using tobacco given the well-established harms associated with tobacco use and second-hand smoke exposure.[230]

Patient discussions

General discussions

- 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 multisystem inflammatory syndrome in children (MIS-C). Reassure the patient that they are likely to feel much better in a week if their symptoms are mild.[405]
- Discuss who to contact if their symptoms get worse, or if MIS-C is suspected. Offer telephone or video consultations as appropriate.[405]
- 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.[405]

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)

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.[1190] Cats showed a greater susceptibility to infection compared with dogs.[1191]
- [CDC: animals and COVID-19] (https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/animals.html)

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.[1192]
- Clinical or subclinical myocarditis has been reported in competitive athletes with recent infection that restricts them from training and competitive play.[1193] However, available evidence does not confirm a causal relationship between COVID-19 and myocardial involvement in athletes.[1194] Early recognition and continuous assessment of cardiac abnormality in competitive athletes is important to prevent cardiac complications.[1195]

General resources

- [WHO: coronavirus disease (COVID-19) pandemic] (https://www.who.int/emergencies/diseases/novel-coronavirus-2019)
- [CDC: COVID-19] (https://www.cdc.gov/coronavirus/2019-nCoV/index.html)
- [NHS England: COVID-19] (https://www.nhs.uk/conditions/coronavirus-covid-19)

Monitoring

Monitoring

Regularly monitor vital signs and laboratory parameters in hospitalized patients to facilitate early recognition of deterioration and monitor for complications.

- 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.[405]
- There is 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.[480]
- 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.[1182] However, it may be more accurate than other scores.[481]

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.[444]
- 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.[1183]
- More than half of patients discharged from hospital had lung function and chest imaging abnormalities 12 weeks after symptom onset.[1184] Pulmonary function tests may reveal altered diffusion capacity, a restrictive pattern, or an obstructive pattern.[1185] 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.[1186]

Prognostic scores

- Various prognostic and clinical risk scores are being researched or developed.
- A living systematic review found that found that QCOVID can be used for risk stratification in the general population, while the PRIEST model, ISARIC4C Deterioration model, Carr's model, and Xie's model are suitable for prognostication in a hospital setting.[1187] The Knight 4C Mortality Score and Wang model also show promise in the hospital setting.[1188] However, there is considerable heterogeneity in the performance of prognostic scores for predicting short-term mortality in hospitalized patients across regions and countries. Only half of the models in one systematic review showed good discrimination when externally validated.[1189]
- Further external validation across various populations is needed before their use can be recommended.

Complications

Complications	Timeframe	Likelihood
post-intensive care syndrome	**variable**	**high**

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. The risk can be minimized with medication management, physical rehabilitation, family support, and follow-up clinics. Physical, mental, or cognitive symptoms were reported frequently in patients who survived 1 year following intensive care unit.[982]

Complications	Timeframe	Likelihood
thrombosis	**variable**	**high**

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.[983] 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).[984]

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.[985] Thromboembolic events are rare in children.[986] The risk factors with the most evidence for being predictive of venous thromboembolism are older age and elevated D-dimer levels.[987] Male sex, obesity, mechanical ventilation, intensive care unit admission, severe parenchymal abnormalities, and elevated white blood cells have also been identified as risk factors.[988] The cumulative incidence of acute pulmonary embolism and deep vein thrombosis among recovered patients after hospital discharge was 1.2% and 2.3%, respectively, much lower compared with the in-hospital incidence.[989] Nonhospitalized patients may also be at increased risk of thromboembolic events.[990]

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.[991] [992] 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).[993] Thrombotic events may be due to cytokine storm, hypoxic injury, endothelial dysfunction, hypercoagulability, and/or increased platelet activity.[994]

Diagnosis: monitor patients for signs or symptoms suggestive of venous or arterial thromboembolism, and proceed according to hospital protocols for diagnosis. Admission D-dimer level has been associated with venous thromboembolism diagnosis during hospitalization; however, there are no optimal thresholds to guide prophylaxis measures.[995] Evaluate hospitalized patients who experience rapid deterioration of pulmonary, cardiac, or neurologic function, or sudden localized loss of peripheral perfusion, for thromboembolic disease.

Management: treat patients with a thromboembolic event (or who are highly suspected to have thromboembolic disease if imaging is not possible) with therapeutic anticoagulation. Follow your local institutional protocols.

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.[630] [631]

FOLLOW UP

Complications	Timeframe	Likelihood
Prognosis: patients with thromboembolic events have 1.93 times the odds of dying compared with patients without venous thromboembolism.[996] Also see Disseminated intravascular coagulation below.		
cardiovascular complications	**variable**	**high**

Cardiovascular complications include arrhythmias, myocardial injury, acute coronary syndrome, and heart failure.[997] While acute infection was associated with a six-fold increase in cardiovascular diagnoses overall, the risk began to decline 5 weeks after infection and returned to baseline levels or below from 12 weeks to 1 year.[998]

Epidemiology: cardiovascular complications have been reported in 14.1% of patients during hospitalization.[997] 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.[999] Higher rates of myocardial injury have been reported in the US (9% to 52%) compared with China (7% to 28%).[1000] A Cochrane review found that the most common cardiovascular complications were arrhythmias, heart failure, and arterial and venous occlusive events.[174] More rarely, cases of fulminant myocarditis, pericarditis, cardiac tamponade, cor pulmonale, and takotsubo syndrome have been reported.[1001] Risk factors include older age, hypertension, underlying cardiovascular disease, and chronic kidney disease.[1000]

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.[1002] [1003]

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.[405]

Management: seek specialist cardiology advice on treatment and follow local treatment protocols.[405] Management of arrhythmias should be based on current guidelines for the respective arrhythmia.[1004] 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.[1005]

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.[405] 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.[1006]

Prognosis: myocardial injury is associated with poor outcomes and survival. Elevated troponin predicts a poor outcome and higher risk of mortality.[1000] An overall case fatality rate of 9.6% has been reported.[997] Infection may have longer-term implications for overall cardiovascular health.[1007] Cardiovascular problems have been reported up to 1 year after infection, including in those who were not hospitalized for the acute infection.[1008]

Complications	Timeframe	Likelihood
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.[405] The risk in critically ill patients with COVID-19 appears to be lower compared with patients with influenza.[1009]

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 (54.2%).[1010] 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.[1011]

Etiology: causes include hemodynamic changes, hypovolemia, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology, or rhabdomyolysis. May be associated with hematuria, proteinuria, and abnormal serum electrolyte levels (e.g., potassium, sodium).[405]

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.[1010] Potassium binders may be used as options alongside standard care for the emergency management of acute life-threatening hyperkalemia.[405] Renal replacement therapy may be required.

Monitoring: monitor patients with chronic kidney disease for at least 2 years after acute kidney injury.[405]

Complications	Timeframe	Likelihood
post-COVID-19 syndrome (long COVID)	**variable**	**medium**

Protracted symptoms are common after many viral and bacterial infections, including SARS-CoV-2 infection.[1012] Case definitions vary, but the World Health Organization (WHO) defines long COVID as a condition that occurs in adults 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.[1013]

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 may include persistent cough, low-grade fever, breathlessness, fatigue, chest pain/tightness, palpitations, myalgia, arthralgia, headaches, vision changes, hearing loss, tinnitus, sore throat, loss of taste/smell, peripheral neuropathy, dizziness, tremors, mood changes, skin rashes, hair loss, sexual dysfunction, gastrointestinal symptoms, neurocognitive difficulties, sleep disturbances, delirium (older people), and mental health conditions.[1014] [1015] [1016] The most common symptoms at 1-year follow-up were fatigue, sweating, chest tightness, anxiety, and myalgia.[1017] Tailor investigations to the clinical presentation, and to rule out any acute or life-threatening complications and alternative diagnoses.

There is a lack of evidence for pharmacologic interventions. A personalized, multidisciplinary rehabilitation plan that covers physical, psychological, and psychiatric aspects of rehabilitation is an important part of management. Give advice and information on self-management including ways to self-manage symptoms. Referral to a specialist may be required in patients where there is clinical concern.[1015] The WHO makes several recommendations for the rehabilitation of adults with post-COVID-19 syndrome.[444] Patients should be monitored closely during treatment. Recovery time differs, but symptoms typically resolve by 12 weeks in most people.

Complications	Timeframe	Likelihood
post COVID-19 vaccination: myocarditis/pericarditis	**variable**	**medium**

Myocarditis or pericarditis may occur following vaccination with mRNA vaccines.[1018] 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 as various mechanisms have been hypothesized.[1019]

Complications	Timeframe	Likelihood

[1020] There is a high likelihood of a causal link, based on autopsy studies.[1021] Cases have also been reported with adenovirus vector vaccines and protein subunit vaccines, albeit more rarely.[1022] [1023]

Epidemiology: the incidence of myocarditis may be as high as 140 to 200 cases per million doses depending on age, sex, and vaccine. Male adolescents and young adults are at the highest risk; the incidence is highest in males ages 12 to 29 years. Myocarditis is more likely with the Moderna vaccine compared with the Pfizer/BioNTech vaccine, and is more likely after the second dose (data for incidence rates after a third dose are limited, although the manufacturer states that the risk profile is similar after the second and third doses). On average, symptom onset was 2 to 4 days after the vaccine dose, although intervals of up to 20 days (or longer) have been reported. Incidence after the second dose may be lower when administered ≥31 days after the first dose compared with ≤30 days among younger age groups. For pericarditis, data were limited but more variation than myocarditis has been reported in patient age, sex, onset timing, and rate of admission to hospital.[1020] [1024] Preliminary real-world data has not picked up an increased risk of myocarditis in children ages 5-11 years as yet.[1025] [1026] Reported rates in immunocompromised people were similar to the general population.[1027] Vaccinated individuals were twice as likely to develop myocarditis/pericarditis in the absence of SARS-CoV-2 infection compared with unvaccinated individuals within a 30-day follow-up period.[1028]

Diagnosis: 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 (note: patients may also present >10 days after vaccination).[1029] The most common presenting symptom was chest pain (34.5%).[1030]

Investigations: order a 12-lead ECG, inflammatory blood markers, complete blood count, and troponin. If ECG or troponin are abnormal, discuss the management plan with the cardiology team. Further investigations (e.g., cardiac imaging and rhythm monitoring) and follow-up should be led by the cardiology team.[1029] The most common findings were ST-related changes on an electrocardiogram (58.7%) and hypokinesia on cardiac magnetic resonance imaging or echocardiography (50.7%). Laboratory findings included elevated troponin I levels (81.7%) and elevated C-reactive protein (71.5%).[1030]

Management: strenuous physical activity should be avoided until symptoms improve.[1029] Patients should be referred to a cardiologist as management depends on the clinical presentation, and guideline-directed therapy is required for complicated cases.[1031]

[UKHSA: myocarditis and pericarditis after COVID-19 vaccination - clinical management guidance for healthcare professionals] (https://www.gov.uk/government/publications/myocarditis-and-pericarditis-after-covid-19-vaccination/myocarditis-and-pericarditis-after-covid-19-vaccination-guidance-for-healthcare-professionals)

Prognosis: up to 93% of adolescents and young adults required hospital admission, with intensive care unit admission required in up to 25% of patients. Median interval from onset to approval for all physical activity was 98 days. Approximately 81% of patients who completed a follow-up healthcare provider survey were considered recovered at follow-up at least 90 days since onset. However, approximately half of patients continued to self-report symptoms (e.g., chest pain), and 25% were prescribed daily cardiac medications.[1032] Severe and potentially fatal myocarditis was reported in 19.8% of all vaccine-related myocarditis cases in one Korean nationwide study, with some patients requiring intensive care unit admission, extracorporeal membrane oxygenation therapy, and heart transplant.[1033]

Consult your local public health authority for guidance on administering further doses of a COVID-19 vaccine. Some countries have implemented age-related prescribing restrictions for mRNA vaccines due to the risk of myocarditis/pericarditis. Modifying mRNA vaccine programs to incorporate age-based product considerations and longer interdose intervals may reduce the risk of myocarditis/pericarditis.[1034]

acute liver injury	variable	medium

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

Complications	Timeframe	Likelihood

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.[1035] Abnormal liver function tests are associated with significantly higher mortality, intensive care unit admission, and mechanical ventilation requirements.[1036] 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.[1037]

Risk factors associated with severe liver injury include older age, preexisting liver disease, and severe disease.[1038] Medications used in the treatment of COVID-19 (e.g., remdesivir, tocilizumab) may have a detrimental effect on liver injury.[1039] Guidelines on the management of liver derangement in patients with COVID-19 have been published.[1040]

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, parkinsonism, cerebral venous sinus thrombosis, myopathy, Guillain-Barre syndrome, dementia, and abnormal findings on brain magnetic resonance imaging.[1041] [1042] [1043] Burning mouth syndrome and burning eye syndrome have been reported.[1044]

Patients commonly have central or peripheral neurologic complications, possibly due to viral invasion of the central nervous system, inflammatory response, or immune dysregulation.[1045] Neurologic complications occur across the lifespan in the context of infection, with and without known comorbidities, and with all disease severities (including asymptomatic patients).[1046] Patients may present with these manifestations, or they may develop them during the course of the disease (usually 1-2 weeks after the onset of respiratory disease).[1047] Patients with preexisting neurologic disorders may develop an exacerbation of their neurologic symptoms.[1048] Long-term sequelae may be possible.[1049] [1050]

Epidemiology: reported in 22% to 35% of patients. Central nervous system manifestations were more common than peripheral nervous system manifestations.[1041] Neurologic involvement is common in children and adolescents (22% in patients ages <21 years).[1051]

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%).[1045] However, the overall absolute incidence of stroke in inpatients has been reported as 0.175%, lower than that reported in previous observational studies.[1052] Patients with severe disease are at an increased risk of ischemic stroke compared with patients with nonsevere disease.[1053] 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.[1054] [1055] Stroke presents later in severe disease, and earlier in mild to moderate disease.[1056] Patients may present with ischemic stroke during the convalescent phase of infection, including younger people age <50 years with asymptomatic or pauci-symptomatic COVID-19.[1057] 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.[1058] Guidelines for the management of acute ischemic stroke in patients with COVID-19 infection have been published.[1059]

Guillain-Barre syndrome: both post-infectious and pre-infectious patterns have been reported.[1045] The pooled prevalence among hospitalized and nonhospitalized patients was 0.15%.[1060] 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.[1061] Patients had an increased odds for demyelinating subtypes. Clinical outcomes were comparable to those for contemporary or historical controls not infected

FOLLOW UP

Complications	Timeframe	Likelihood

with SARS-CoV-2.[1060] Guillain-Barre syndrome has also been associated with the administration of COVID-19 vaccines.[1062]

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.[1063] Rare cases of autoimmune encephalitis have been reported.[1064]

The key to the management of neurologic complications is a detailed history and exam, together with the appropriate interpretation of laboratory and radiologic data. In most cases, management of these conditions should follow pre-COVID-19 guidance.[1065]

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 age 45 years.[1066]

pregnancy-related complications	variable	medium

Pregnancy outcome is usually good, although there are little data on exposure during early pregnancy.[220] The risk for complications was higher in pregnant women who were symptomatic.[1067] The risk of maternal and neonatal complications appeared to be substantially less during the Omicron-dominant period compared with the pre-Omicron period.[1068] Lower-income countries have reported higher rates of maternal intensive care unit admission and mortality, and stillbirths, compared with higher-income countries.[1069]

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.[218] [219] [1070] 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.[1071]

Miscarriage: there is no evidence that infection in the first or second trimesters increases the risk of miscarriage. However, further research is required.[1072]

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.[218] [219] [1070]

Stillbirth and neonatal death: the overall rates of stillbirths and neonatal deaths do not appear to be higher than the background rates.[218] [219] [1073] [1074] However, data are conflicting. In England, there was 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.[1075] 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.[1076] A Scandinavian registry study also found an increased risk of stillbirth after 22 weeks' gestation, particularly in women infected with the

Complications	Timeframe	Likelihood
Delta variant.[1077] An individual participant data meta-analysis found no link between infection during pregnancy with an increased risk of stillbirth at or beyond 28 weeks' gestation or with intrauterine growth restriction.[1078] Another meta-analysis found an increased risk of stillbirth.[1079] 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.[218] [219] [1070] [1080] [1081] Neonatal outcomes: there is limited and conflicting evidence of an increased risk of short- or long-term neonatal morbidity (e.g., respiratory disease), and further research is required.[1074] There is some evidence that maternal infection and perinatal transmission has the potential to affect the auditory system of the newborn, especially during the second and third trimester of pregnancy. However, data are limited and inconsistent and further research is required.[1082] A Nordic registry-based study found infection during the first trimester was not associated with a risk of major congenital anomalies among infants.[1083]		
sepsis/septic shock	**variable**	**low**
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.[1084] Guidelines for the management of shock in critically ill patients with COVID-19 recommend a conservative fluid strategy and a vasoactive agent. Norepinephrine (noradrenaline) is the preferred first-line agent in adults (epinephrine [adrenaline] or norepinephrine may be used in children). Vasopressin or epinephrine (adrenaline) can be added to norepinephrine in adults if target mean arterial pressure cannot be achieved with norepinephrine alone.[715] Consult your local guidelines for more information.		
disseminated intravascular coagulation	**variable**	**low**
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.[1085] 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.[1086] 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.[1087] 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 (IL)-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.[1088] 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.[1089] In patients with heparin-induced thrombocytopenia (or a history of it), argatroban or bivalirudin are recommended.[1085] 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.[1088] [1090]		

Complications	Timeframe	Likelihood
acute respiratory failure	**variable**	**low**
The leading cause of death is respiratory failure from acute respiratory distress syndrome.[900] The overall pooled prevalence of COVID-19-induced acute respiratory distress syndrome was 32% globally.[1091] Children can quickly progress to respiratory failure.[1092] 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%.[1093]		
air leak	**variable**	**low**
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 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.[1094]		
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 (IL)-6, have been identified in these patients. Features of secondary hemophagocytic lymphohistiocytosis may be present. Treatment options include IL-6 inhibitors (e.g., tocilizumab), Janus kinase (JAK) inhibitors (e.g., baricitinib), and anakinra.[1095] Also see Pediatric inflammatory multisystem syndrome, a cytokine release syndrome-like illness in children, below.		
multisystem inflammatory syndrome in children (MIS-C)	**variable**	**low**
Also known as pediatric inflammatory multisystem syndrome (PIMS), 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.[1096] 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.[1097] 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.[438] [1098] Three distinct phenotypic subtypes have been observed.[1099] Can occur rarely after COVID-19 vaccination.[1100] [1101] Epidemiology: the risk of MIS-C within 2 months of confirmed infection was 0.05% in one Danish cohort study.[1102] The risk decreased in the second year of the pandemic and decreased with evolution of the SARS-CoV-2 variant.[1103] MIS-C continued to occur in 2023, but at low rates compared with early in the pandemic.[1104] A systematic review found that the median age of patients was age 7.8 years of , and 60% of patients were male. Obesity was the most common comorbidity, followed by respiratory diseases, prematurity, and asthma.[1105] Risk factors for developing MIS-C include male sex, age 5 to		

Complications	Timeframe	Likelihood

11 years, foreign-born parents, asthma, obesity, and life-limiting conditions.[1106] 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 (IL)-6; and reduced lymphocyte or platelet counts.[1107] 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.[1108] There appears to be a lower risk of MIS-C with the Omicron variant.[1109]

Diagnosis: patients often have predominant cardiac dysfunction and gastrointestinal symptoms. The most common manifestations were fever (99%), gastrointestinal symptoms (77%), and dermatologic symptoms (63%).[1105] The pooled prevalence of significant left ventricular dysfunction was 38%, coronary aneurysm or dilatation was 20%, and ECG abnormalities/cardiac arrhythmias was 28%.[1110] Neonates commonly present with cardiorespiratory compromise.[1108] Approximately 20% of children develop acute kidney injury.[1111] 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.[1112] Patients with MIS-C presented more frequently with respiratory and gastrointestinal symptoms and shock compared with patients with Kawasaki disease; however, they had a lower incidence of conjunctivitis.[1113] Disease may be less severe after infection with the Omicron variant compared with Alpha and Delta variants.[1114]

Investigations: inflammatory, coagulation, and cardiac markers were elevated in the majority of patients.[1105] 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.[1110]

Management: management is mainly supportive and involves a multidisciplinary team. Approximately 53% of patients required intensive care admission.[1105] The optimal choice and combination of immunomodulating therapies have not been definitively established. The World Health Organization (WHO) 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.[444] In the US, the Infectious Diseases Society of America (IDSA) recommends initial therapy with intravenous immune globulin and/or a corticosteroid. Anakinra, tocilizumab, or infliximab may be used in refractory cases.[401] Guidance has also been published by the American College of Rheumatology.[1115] 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.[1116] 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.[1117] The mortality rate was 3.9%.[1105]

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 may be a precaution for vaccination. Consult your local guidelines for more information.

post COVID-19 vaccination: vaccine-induced immune thrombocytopenia and thrombosis (VITT) and other thromboembolic events	**variable**	**low**

VITT is also known as thrombosis with thrombocytopenia syndrome (TTS) and vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). Adenovirus-vector vaccines, the cause of VITT, are no longer available in most countries.

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. Thrombosis occurs in uncommon sites (e.g., cerebral venous sinus thrombosis,

Complications	Timeframe	Likelihood

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.[1118] [1119] Cases have also been reported with mRNA vaccines, albeit more rarely.[1120] [1121] [1122]

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.[1123] In the US, the overall risk with the Janssen vaccine was estimated to be 3.83 cases per million people who received 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), and a case fatality rate of 15%.[1124] Cases have been reported up to 48 days after vaccination.[1125]

Diagnosis: advise adenovirus-vector vaccine recipients who experience any severe symptoms from around 4 to 20 days (or longer) after vaccination to seek urgent medical attention.[1126] Approximately half of patients present with cerebral venous sinus thrombosis.[1127] Headache is the most common presenting symptom, and may precede VITT by several days.[1128] [1129] Patients may rarely present with ischemic stroke.[1130] [1131] 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 42 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 signs and 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.[1132] [1133] [1134]

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.

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 (other than emergency situations), heparin (including heparin flushing solution), low molecular weight heparin, and vitamin K antagonists (e.g., warfarin). Heparin may be used if nonheparin-based anticoagulants are not available. Consider plasma exchange, fibrinogen replacement, or rituximab in select patients. Some patients may require surgery to treat thrombosis.[1132] [1133] [1134][1135]

Prognosis: mortality due to complications has been reported to be 39%.[1128] Fibrinogen levels, age, platelet count, and the presence of intracerebral hemorrhage or cerebral venous thrombosis are significantly associated with an increased risk of mortality.[1136] Consult local guidelines for advice on further vaccination after an episode of VITT.

Thromboembolic events that are distinct from VITT may occur after vaccination with any COVID-19 vaccine, but most commonly occur after vaccination with adenovirus-vector vaccines. Venous thrombosis was more common than arterial thrombosis. Cerebral venous thrombosis was the most common

Complications	Timeframe	Likelihood
manifestation in patients with venous thrombosis, followed by deep vein thrombosis. Myocardial infarction was common in patients with arterial thrombosis, followed by ischemic stroke.[1137] Adenovirus-vector vaccines may be associated with an increased incidence of pulmonary embolism and myocardial infarction in the second week after vaccination.[1138]		
aspergillosis	**variable**	**low**
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.[405] Epidemiology: reported in 10.2% of patients admitted to the intensive care unit in one study.[1139] Risk factors include older age, chronic lung disease (including preexisting COPD), chronic liver disease, hematologic malignancies, cerebrovascular disease, renal replacement therapy, mechanical ventilation, immunosuppression, receipt of interleukin (IL)-6 inhibitors, and use of high-dose corticosteroids.[405] [1140] [1141][1142] Diagnosis: consider diagnosis in patients who deteriorate despite optimal supportive care or who have other suspicious radiologic or clinical features.[405] [1140] 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).[405] Frequently manifests as COVID-19 pneumonia without the common computed tomography scan abnormalities of pulmonary aspergillosis.[1143] 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.[405] 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.[405] Refer to your local protocols on the management of CAPA. Prognosis: a mortality rate of approximately 55% has been reported.[1139] [1141]		
mucormycosis	**variable**	**low**
Mucormycosis (also known as "black fungus") has been reported rarely, particularly in low- and middle-income countries, predominantly India.[1144] COVID-19-associated pulmonary mucormycosis is diagnosed either simultaneously with, or within 3 months of, virologically confirmed COVID-19. Case definitions for proven, probable, or possible pulmonary disease have been published. Coinfection with aspergillosis is possible.[1145] Epidemiology: approximately 88% of cases were reported from low- or middle-income countries.[1146] Cases in India increased significantly during its second wave in early 2021.[1147] Cases have been reported in other countries, including the US.[1148] Risk factors include male sex, uncontrolled diabetes, and immunosuppression (e.g., due to corticosteroid therapy).[1149] [1150] 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.[1151] 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%).[1149] Cases of atypical-site mucormycosis have been reported, as well as cases in COVID-19 recovered patients.[1152] [1153] Do not hesitate to aggressively order investigations as appropriate for detecting fungal etiology.[1151] Flexible bronchoscopy and chest imaging are recommended to enable early diagnosis of pulmonary mucormycosis.[1145]		

FOLLOW UP

Complications	Timeframe	Likelihood
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.[1145] [1151] 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.[1151] Complications: rare cases of pulmonary artery pseudoaneurysm have been reported with COVID-19-associated pulmonary mucormycosis.[1154] Prognosis: overall mortality rate has been reported to be 39%.[1146] The 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.[1147] Risk factors for increased mortality includes older age, specific comorbidities, aspergillus coinfection, and use of tocilizumab.[1146] A significant proportion of survivors had life-changing morbidities (e.g., vision loss).[1144] Patients with pulmonary and rhino-orbito-cerebral mucormycosis and those who receive medical treatment only are at increased risk for mortality.[1155]		
candidemia	**variable**	**low**
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.[1156] Cases of candidemia due to *Candida auris* , an emerging multidrug-resistant pathogen, have been reported.[1157] 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.[1158]		
pancreatic injury	**variable**	**low**
Mild pancreatic injury (defined as elevated serum amylase or lipase levels) has been reported in 17% of patients in one case series.[1159] 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.[1160] Patients with acute pancreatitis had a high pooled mortality (18.5%) and significantly worse clinical outcomes.[1161] The most common presenting symptom was abdominal pain.[1162] Prior history of pancreatitis does not appear to be a risk factor for pancreatic inflammation in patients with COVID-19.[1163] A causal relationship between SARS-CoV-2 infection and acute pancreatitis has not been established.[1164]		
immune thrombocytopenia	**variable**	**low**
Immune thrombocytopenia has been reported rarely. The majority of cases were in patients age >50 years, 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.[1165]		
thyroid disorders	**variable**	**low**
Subacute thyroiditis is a thyroid disease of viral or post-viral origin. Evidence suggests that infection with SARS-CoV-2 may trigger subacute thyroiditis, based on case reports and case studies.[1166] A review of		

Complications	Timeframe	Likelihood

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.[1167]

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.[1168]

gastrointestinal complications	**variable**	**low**

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.[1169] In patients with acute mesenteric ischemia, small-bowel ischemia was the most prevalent finding on abdominal computed tomography, followed by ischemic colitis. Nonocclusive mesenteric ischemia was the most common pattern of bowel involvement.[1170]

Macrovascular 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.[1171] Patients with intestinal ischemia generally present with abdominal pain and vomiting. Management includes gastric decompression, fluids, hemodynamic support, and surgery.[1172]

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%.[1173] Risk factors for gastrointestinal hemorrhage in COVID-19 patients include history of gastrointestinal bleeding and anticoagulant use.[1174]

acute hair loss	**variable**	**low**

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.[1175] Cases of new-onset alopecia areata, as well as recurrences or exacerbations, have also been reported after infection.[1176]

lower urinary tract complications	**variable**	**low**

There is 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 (including decreased sperm count, sperm concentration, sperm motility, and normal sperm morphology; decreased circulating testosterone level); bladder hemorrhage; acute urinary retention; and worsening of existing lower urinary tract symptoms (including exacerbation of benign prostatic hyperplasia). Semen parameters appear to return to normal as patients recover. Further research is required.[1177] [1178] [1179][1180] [1181]

parosmia	**variable**	**low**

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

Complications	Timeframe	Likelihood
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.[586]		

Prognosis

Mortality

The leading cause of death is respiratory failure from acute respiratory distress syndrome (ARDS).[900]

- The overall pooled mortality rate from ARDS in COVID-19 patients was 39%; however, this varied significantly between countries (e.g., China 69%, Iran 28%, France 19%, Germany 13%).[901]
- 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.[902]
- 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.[903]
- Other common causes of death include sepsis or septic shock, sepsis-related multiorgan failure, bacterial or viral coinfections, venous thromboembolism, and cardiac failure.[904]

Mortality rate depends on age and the presence of underlying medical conditions.

- People age <65 years had a very small risk of death even in pandemic epicenters, and deaths in people age <65 years without any underlying conditions was rare.[905]
- Deaths in children and young people are rare. A systematic review and meta-analysis found that 3.3% of children were hospitalized, 0.3% were admitted to the intensive care unit, and 0.02% died in community-based studies (23.9%, 2.9%, and 0.2%, respectively, in hospital-based screening studies).[906]
- 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] The three most prevalent comorbidities in deceased patients were hypertension, diabetes mellitus, and respiratory disease.[907]

Mortality rates are high in critically ill patients.

- Global all-cause mortality was 35% in the intensive care unit and 32% in hospital for critically ill patients for the year 2020. However, mortality rates varied between regions. For example, the mortality was as high as 48% in Southeast Asia and as low as 15% in America.[908]
- A systematic review and meta-analysis of data up to 31 December 2021 found that in critically ill patients who required intensive care, the in-hospital case fatality rate (CFR), intensive care unit CFR, mechanical ventilation CFR, renal replacement therapy CFR, and extracorporeal membrane oxygenation (ECMO) CFR was 25.9%, 37.3%, 51.6%, 66.1%, and 58%, respectively. Overall, mechanical ventilation mortality decreased significantly since the start of the pandemic (52.7% to 31.3%).[909]

Mortality rates have decreased over time despite stable patient characteristics.

- 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.[910] 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.[911]
- Mortality rates decreased sharply in the US over the first 6 months of the pandemic.[912] [913] 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.[914] 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.[915]

- Overall global hospital mortality was 16% for general patients admitted to hospital for COVID-19; however, rates varied according to geographic area.[916]
- This decrease in mortality rate 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 (HFNO) 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 was estimated that approximately 1.5 to 2 billion infections occurred globally as of February 2021, with an estimated overall IFR of 0.15%. There were substantial differences in IFR and infection spread across continents, countries, and locations.[917] Data suggested 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).[918]
- The Centers for Disease Control and Prevention (CDC) estimated the IFR in 2021, according to age, to be:[919]
  - 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 age <65 years was 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 could be made, the IFR was 0.85%. However, all deaths occurred in patients age >70 years, and the rate in a younger, healthier population would be much lower.[920]

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.[921]
- The World Health Organization (WHO) currently estimates that the global CFR is approximately 0.9% (as of 2 February 2025).[17] CFR varies considerably between countries. The pooled CFR in the general population in a systematic review and meta-analysis was 1%.[922] 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%.[29]
- 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%).[129]
  - In China, the majority of deaths were in patients ages ≥60 years.[923] 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%).[924]
  - 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%).[925]
  - Deaths are rare in children.[21] [129] 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.[926]

- 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).[923]
- CFR increases with disease severity.
    - The pooled CFR in hospitalized patients was 13%.[922] The CFR is highest in patients with critical disease, ranging from 26% to 67% in studies.[923] [927] [928]
- CFR is lower with the Omicron variant.
    - The Omicron variant had a lower CFR compared with the Delta variant.[929] [930]

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.[931] Estimates of the IFR/CFR decreased considerably over the course of the pandemic.
- A positive polymerase chain reaction (PCR) result was 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.[932] [933]
- Patients who died "with" COVID-19 and patients who died "from" COVID-19 were 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.[931] [934]

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:[935] [936] [937] [938] [939] [940] [941]

- 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
    - 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
    - $PaO_2/FiO_2 \leq 200$ 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.[942]

During the Omicron era, the risk of hospitalization and death was increased in patients with COPD, cerebrovascular disease, diabetes mellitus, respiratory or heart diseases, and heart failure. The risk of intensive care unit admission was increased in patients with obesity and diabetes.[943]

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.[944]

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.[945]

Persistent infections have been reported in immunocompromised people.[946]

The risk of severe post-acute complications in patients who were not admitted to hospital for the primary infection appears to be low. However, these patients 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 primary care physician 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.[947]

Reinfection

Reinfection refers to a new infection following previous confirmed infection (i.e., 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.[948]

Cases of reinfection are rare.

- A systematic review and meta-analysis reported the pooled reinfection rate to be 0.65% in the pre-Omicron period. The rate was higher in high-risk populations (1.6%), and the rate of symptomatic reinfection was lower (0.4%).[949] 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.[950]
- The risk of reinfection increased during the early Omicron period.[490] [951] Although the reinfection rates increased, the risk of severe disease was very low.[952]
- No significant differences in clinical presentation or disease severity have been noted between primary infection and reinfection.[953]

Consider reinfection in the following circumstances:[948]

- 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.[948]

Management

- Manage patients with suspected reinfection as if they are infectious, as for a new or first infection. It is important to note that illness due to reinfection may not necessarily follow the same clinical course as the previous episode.[948]

Immunity

The global population has varied immune histories to SARS-CoV-2 derived from various exposures to infection, virus variants, and vaccination.

The immune response to SARS-CoV-2 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.[954]

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.[955] [956]
- 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.[957]
- Maternal IgG antibodies to SARS-CoV-2 have been found to transfer across the placenta after infection in pregnant women.[958]

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.[959]
- 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.[960] [961]
- Data suggest that T-cell responses are largely unaffected by SARS-CoV-2 variants.[962] [963]

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.[964] Convalescent critically ill patients consistently generated substantial adaptive and humoral immune responses against SARS-CoV-2 for more than 1 year after hospital discharge.[965]
- Meta-analyses have found a high (84% to 87%) level of protection after natural infection that persisted for at least 1 year.[966] [967] Protection against all outcomes (infection, symptomatic disease, severe disease) from pre-Omicron variants was very high (>85% on average) and remained high after 40 weeks. Protection against severe disease caused by the early Omicron variants was also high (88.9%), but protection against reinfection or symptomatic disease was much lower (<55%) compared with pre-Omicron variants.[968]
- Infection with the Omicron variant has been found to induce strong immune protection against a subsequent Omicron infection, regardless of the subvariant.[969] [970] [971] An additional earlier infection with a non-Omicron variant was found to strengthen this protection against a subsequent Omicron infection in one study.[972]

Preexisting immunity to SARS-CoV-2

- Testing of blood samples taken before the COVID-19 pandemic showed that some people already had immune cells that recognized SARS-CoV-2. Studies reported T-cell reactivity against SARS-CoV-2 in 20% to 50% of people with no known exposure to the virus.[973] Approximately 5% of uninfected adults and 62% of uninfected children aged 6 to 16 years had antibodies that recognized SARS-CoV-2 in one study.[974]
- 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.
- Observational evidence suggested that prior infection with SARS-CoV-1 was associated with detectable levels of antibodies that cross-reacted and neutralized SARS-CoV-2.[975]

Natural versus vaccine-induced immunity

- Evidence suggested that natural immunity conferred at least equal or longer-lasting and stronger protection against infection, symptomatic disease, and hospitalization caused by the Delta variant compared with vaccine-induced immunity.[976]
- Protection associated with natural infection waned with time after primary infection and reached approximately 70% by the 16th month (in the pre-Omicron period). This is similar to vaccine immunity, but occurs at a slower rate. Immune evasion of Omicron subvariants reduced the overall protection of pre-Omicron natural immunity and accelerated its waning, again, similar to vaccine immunity but at a slower rate. Protection of natural infection against severe reinfection remains strong with no evidence for waning (regardless of variant) for over 14 months after primary infection.[977]
- Previous natural infection has been associated with a lower incidence of infection, regardless of the variant, compared with the primary series of mRNA vaccination.[978]
- Hybrid immunity (immunity developed through a combination of infection and vaccination) provides higher and more sustained protection (including against severe disease and hospital admission) against reinfection than either vaccination or infection alone, regardless of the variant or mRNA vaccine type.[979] [980] [981]

Diagnostic guidelines

International

Overview of testing for SARS-CoV-2 (https://www.cdc.gov/covid/hcp/clinical-care/overview-testing-sars-cov-2.html) [442]

Published by: Centers for Disease Control and Prevention **Last published:** 2024

Infection control guidance: SARS-CoV-2 (https://www.cdc.gov/covid/hcp/infection-control/index.html) [665]

Published by: Centers for Disease Control and Prevention **Last published:** 2024

Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: serologic testing (https://www.idsociety.org/practice-guideline/all-practice-guidelines) [507]

Published by: Infectious Diseases Society of America **Last published:** 2024

Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: molecular diagnostic testing (https://www.idsociety.org/practice-guideline/all-practice-guidelines) [614]

Published by: Infectious Diseases Society of America **Last published:** 2023

Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: antigen testing (https://www.idsociety.org/practice-guideline/all-practice-guidelines) [615]

Published by: Infectious Diseases Society of America **Last published:** 2022

Infectious Diseases Society of America guidelines on infection prevention for healthcare personnel caring for patients with suspected or known COVID-19 (https://www.idsociety.org/practice-guideline/all-practice-guidelines) [666]

Published by: Infectious Diseases Society of America **Last published:** 2021

Public health surveillance for COVID-19: interim guidance (https://www.who.int/publications/i/item/WHO-2019-nCoV-SurveillanceGuidance-2022.2) [124]

Published by: World Health Organization **Last published:** 2022 (addendum 2023)

Use of SARS-CoV-2 antigen-detection rapid diagnostic tests for COVID-19 self-testing (https://www.who.int/publications/i/item/WHO-2019-nCoV-Ag-RDTs-Self_testing-2022.1) [503]

Published by: World Health Organization **Last published:** 2022

Antigen-detection in the diagnosis of SARS-CoV-2 infection: interim guidance (https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays) [440]

Published by: World Health Organization **Last published:** 2021

International

Diagnostic testing for SARS-CoV-2: interim guidance (https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2) [439]

Published by: World Health Organization **Last published:** 2020

Use of chest imaging in COVID-19: a rapid advice guide (https://www.who.int/publications/i/item/use-of-chest-imaging-in-covid-19) [544]

Published by: World Health Organization **Last published:** 2020

Coronavirus (COVID-19): guidance (https://www.gov.uk/government/collections/coronavirus-covid-19-list-of-guidance) [667]

Published by: UK Health Security Agency **Last published:** 2024

ESCMID COVID-19 guidelines: diagnostic testing for SARS-CoV-2 (https://www.escmid.org/guidelines-journals/guidelines/published-guidelines) [668]

Published by: European Society of Clinical Microbiology and Infectious Diseases **Last published:** 2022

GUIDELINES

Treatment guidelines

International

COVID-19 treatment clinical care for outpatients (https://www.cdc.gov/covid/hcp/clinical-care/outpatient-treatment.html) [887]

Published by: Centers for Disease Control and Prevention **Last published:** 2025

COVID-19: clinical considerations for special populations (https://www.cdc.gov/covid/hcp/clinical-care/considerations-special-groups.html) [888]

Published by: Centers for Disease Control and Prevention **Last published:** 2025

CDC yellow book: health information for international travel - COVID-19 (https://www.cdc.gov/yellow-book/index.html) [889]

Published by: Centers for Disease Control and Prevention **Last published:** 2025

Interim clinical considerations for use of COVID-19 vaccines in the United States (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html) [890]

Published by: Centers for Disease Control and Prevention **Last published:** 2025

Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19 (https://www.idsociety.org/practice-guideline/all-practice-guidelines) [401]

Published by: Infectious Diseases Society of America **Last published:** 2025

COVID-19: clinical course - progression, management, and treatment (https://www.cdc.gov/covid/hcp/clinical-care/management-and-treatment.html) [670]

Published by: Centers for Disease Control and Prevention **Last published:** 2024

Coronavirus disease 2019 (COVID-19) (https://www.acponline.org/clinical-information/clinical-guidelines-recommendations) [891]

Published by: American College of Physicians **Last published:** 2024

Clinical management of COVID-19: living guideline (https://www.who.int/publications/i/item/B09467) [444]

Published by: World Health Organization **Last published:** 2025

Therapeutics and COVID-19: living guideline (https://www.who.int/publications/i/item/B09540) [406]

Published by: World Health Organization **Last published:** 2025

COVID-19 outbreak toolbox (https://www.who.int/emergencies/outbreak-toolkit/disease-outbreak-toolboxes/covid-19-outbreak-toolbox) [892]

Published by: World Health Organization **Last published:** 2024

International

Drugs to prevent COVID-19: WHO living guideline (https://www.who.int/publications/i/item/WHO-2019-nCoV-prophylaxes-2023.1) [404]

Published by: World Health Organization **Last published:** 2023

Surviving Sepsis Campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU (https://www.sccm.org/clinical-resources/guidelines/guidelines/surviving-sepsis-campaign-guidelines-on-the-manage) [715]

Published by: Surviving Sepsis Campaign **Last published:** 2021

Home care for patients with suspected or confirmed COVID-19 and management of their contacts: interim guidance (https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts) [669]

Published by: World Health Organization **Last published:** 2020

COVID-19 rapid guideline: managing COVID-19 (https://www.nice.org.uk/guidance/ng191) [405]

Published by: National Institute for Health and Care Excellence (UK) **Last published:** 2025

Nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19 (https://www.nice.org.uk/guidance/ta878) [681]

Published by: National Institute for Health and Care Excellence (UK) **Last published:** 2025

Molnupiravir for treating COVID-19 (https://www.nice.org.uk/guidance/ta1056) [682]

Published by: National Institute for Health and Care Excellence (UK) **Last published:** 2025

COVID-19: the green book, chapter 14a (https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a) [893]

Published by: UK Health Security Agency **Last published:** 2025

Coronavirus (COVID-19): guidance (https://www.gov.uk/government/collections/coronavirus-covid-19-list-of-guidance) [667]

Published by: UK Health Security Agency **Last published:** 2024

Remdesivir and tixagevimab plus cilgavimab for treating COVID-19 (https://www.nice.org.uk/guidance/ta971) [701]

Published by: National Institute for Health and Care Excellence (UK) **Last published:** 2024

Coronavirus disease 2019 (COVID-19) (https://www.health.gov.au/resources/collections/cdna-series-of-national-guidelines-songs) [894]

Published by: Australian Government Department of Health and Aged Care; Australian Centre for Disease Control **Last published:** 2024

GUIDELINES

International

European Society of Clinical Microbiology and Infectious Diseases guidelines for coronavirus disease 2019: an update on treatment of patients with mild/moderate disease (https://www.escmid.org/guidelines-journals/guidelines/published-guidelines) [895]

Published by: European Society of Clinical Microbiology and Infectious Diseases **Last published:** 2022

Coronavirus (COVID-19) infection in pregnancy (https://www.rcog.org.uk/coronavirus-pregnancy) [896]

Published by: Royal College of Obstetricians and Gynaecologists (UK) **Last published:** 2022

Care for adults with COVID-19: living guidelines (https://onlinelibrary.wiley.com/doi/10.5694/mja2.51718) [897]

Published by: Australian National COVID-19 Clinical Evidence Taskforce **Last published:** 2022

Prevention and management of venous thromboembolism in patients with COVID-19 (https://www.sign.ac.uk/our-guidelines) [898]

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2021

Management of hospitalised adults with coronavirus disease 2019 (COVID-19) (https://channel.ersnet.org/channel-25-guidelines) [899]

Published by: European Respiratory Society **Last published:** 2021

GUIDELINES

Online resources

1. WHO: tracking SARS-CoV-2 variants (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants) *(external link)*

2. UKHSA: SARS-CoV-2 - genome sequence prevalence and growth rate (https://www.gov.uk/government/publications/sars-cov-2-genome-sequence-prevalence-and-growth-rate) *(external link)*

3. CDC: variants and genomic surveillance (https://www.cdc.gov/covid/php/variants/variants-and-genomic-surveillance.html) *(external link)*

4. WHO: COVID-19 dashboard (https://data.who.int/dashboards/covid19/cases?n=c) *(external link)*

5. CDC: surveillance and data analytics (https://www.cdc.gov/covid/php/surveillance/index.html) *(external link)*

6. BMJ: visualising SARS-CoV-2 transmission routes and mitigations (https://www.bmj.com/content/375/bmj-2021-065312) *(external link)*

7. WHO: COVID-19 vaccines technical documents (https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials) *(external link)*

8. UK Health Security Agency: COVID-19 - the green book, chapter 14a (https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a) *(external link)*

9. CDC: interim clinical considerations for use of COVID-19 vaccines in the United States (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html) *(external link)*

10. WHO: infection prevention and control in the context of COVID-19 - a guideline (https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC-guideline-2023.4) *(external link)*

11. CDC: infection control guidance - SARS-CoV-2 (https://www.cdc.gov/covid/hcp/infection-control/index.html) *(external link)*

12. WHO: advice for the public – coronavirus disease (COVID-19) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public) *(external link)*

13. The BMJ Clinical Review: the role of masks and respirators in preventing respiratory infections in healthcare and community settings (https://www.bmj.com/content/388/bmj-2023-078573) *(external link)*

14. BMJ practice pointer: remote management of covid-19 using home pulse oximetry and virtual ward support (https://www.bmj.com/content/372/bmj.n677) *(external link)*

15. CDC: overview of testing for SARS-CoV-2 (https://www.cdc.gov/covid/hcp/clinical-care/overview-testing-sars-cov-2.html) *(external link)*

ONLINE RESOURCES

16. BMJ practice pointer: testing for SARS-CoV-2 antibodies (https://www.bmj.com/content/370/bmj.m3325) *(external link)*

17. BMJ practice pointer: interpreting a covid-19 test result (https://www.bmj.com/content/369/bmj.m1808) *(external link)*

18. 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) *(external link)*

19. BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas (https://www.bsti.org.uk/media/resources/files/Lung_US_print_out_and_scoring_proforma.pdf) *(external link)*

20. BMJ: interpreting a lateral flow SARS-CoV-2 antigen test (https://www.bmj.com/content/373/bmj.n1411) *(external link)*

21. NHS England: 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) *(external link)*

22. WHO: public health surveillance for COVID-19 – interim guidance (https://www.who.int/publications/i/item/who-2019-nCoV-surveillanceguidance-2020.7) *(external link)*

23. CDC: coronavirus disease 2019 (COVID-19) 2023 case definition (https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2023) *(external link)*

24. ECDC: case definition for COVID-19 (https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition) *(external link)*

25. 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#what-to-do-if-you-have-a-positive-covid-19-test-result) *(external link)*

26. CDC: preventing spread of respiratory viruses when you're sick (https://www.cdc.gov/respiratory-viruses/prevention/precautions-when-sick.html) *(external link)*

27. WHO: home care for patients with suspected or confirmed COVID-19 and management of their contacts (https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts) *(external link)*

28. COVID-19 LNMA (living network meta-analysis) (https://www.covid19lnma.com) *(external link)*

29. Clinical Frailty Scale (https://www.dal.ca/sites/gmr/our-tools/clinical-frailty-scale.html) *(external link)*

30. IDSA: management of drug interactions with nirmatrelvir/ritonavir (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/management-of-drug-interactions-with-nirmatrelvirritonavir-paxlovid) *(external link)*

ONLINE RESOURCES

31. BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19 (https://www.bmj.com/content/370/bmj.m3379) *(external link)*
32. RECOVERY trial (https://www.recoverytrial.net) *(external link)*
33. WHO: COVID-19 Solidarity therapeutics trial (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments) *(external link)*
34. UKHSA: myocarditis and pericarditis after COVID-19 vaccination - clinical management guidance for healthcare professionals (https://www.gov.uk/government/publications/myocarditis-and-pericarditis-after-covid-19-vaccination/myocarditis-and-pericarditis-after-covid-19-vaccination-guidance-for-healthcare-professionals) *(external link)*
35. Health Education England: adult pulse oximetry monitoring video (https://www.youtube.com/watch?v=ifnYjD4IKus&t=141s) *(external link)*
36. CDC: animals and COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/animals.html) *(external link)*
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Key articles

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- National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing COVID-19. May 2025 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng191)
- World Health Organization. Therapeutics and COVID-19: living guideline, August 2025. Sep 2025 [internet publication]. Full text (https://www.who.int/publications/i/item/B09540)
- World Health Organization. Clinical management of COVID-19: living guideline, June 2025. Jul 2025 [internet publication]. Full text (https://www.who.int/publications/i/item/B09467)

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Images

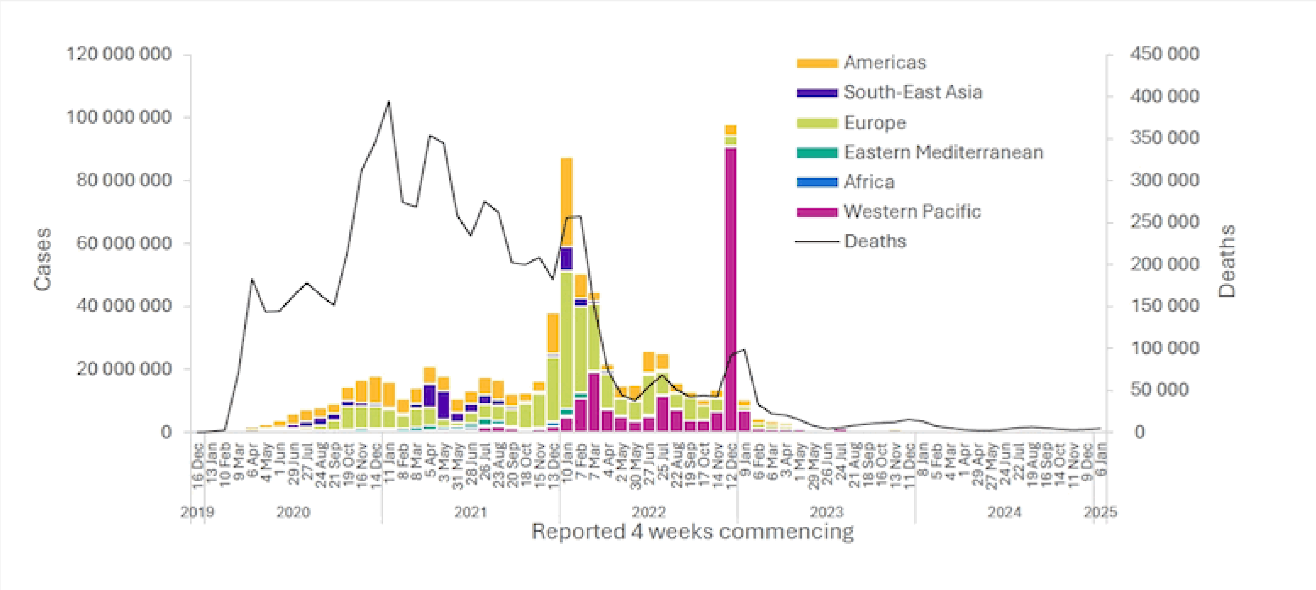

Figure 1: Number of COVID-19 cases reported weekly by WHO Region, and global deaths, as of 2 February 2025

World Health Organization

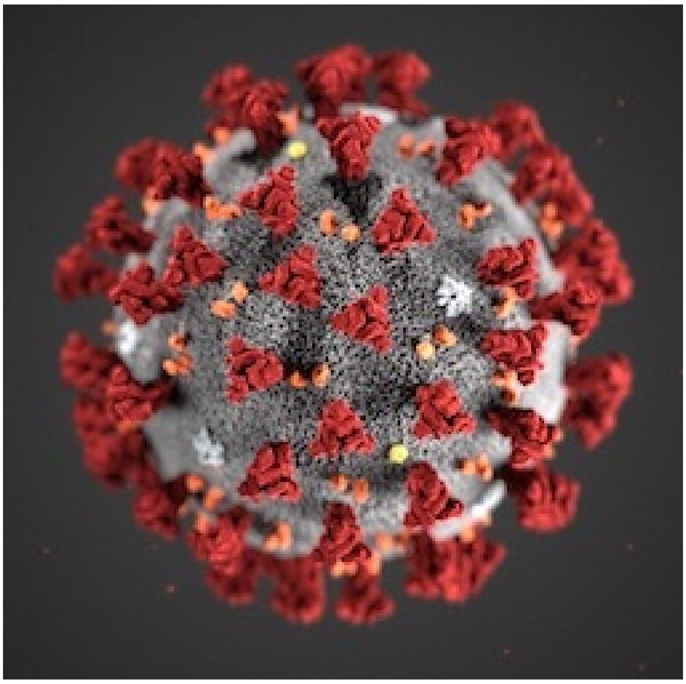

Figure 2: Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically

Centers for Disease Control and Prevention

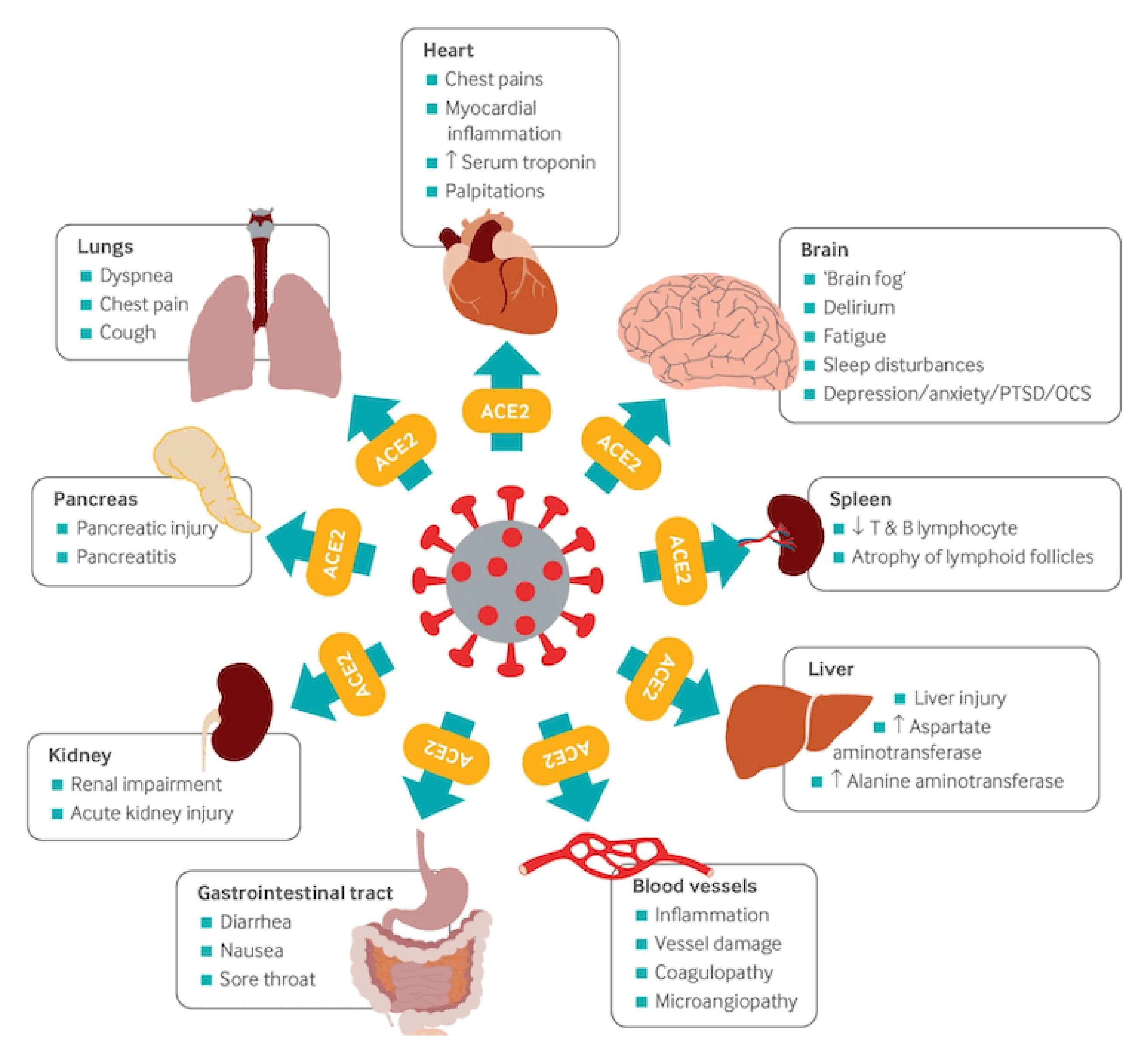

Figure 3: Multi-organ complications of COVID-19 and long COVID. The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor

BMJ. 2021;374:n1648

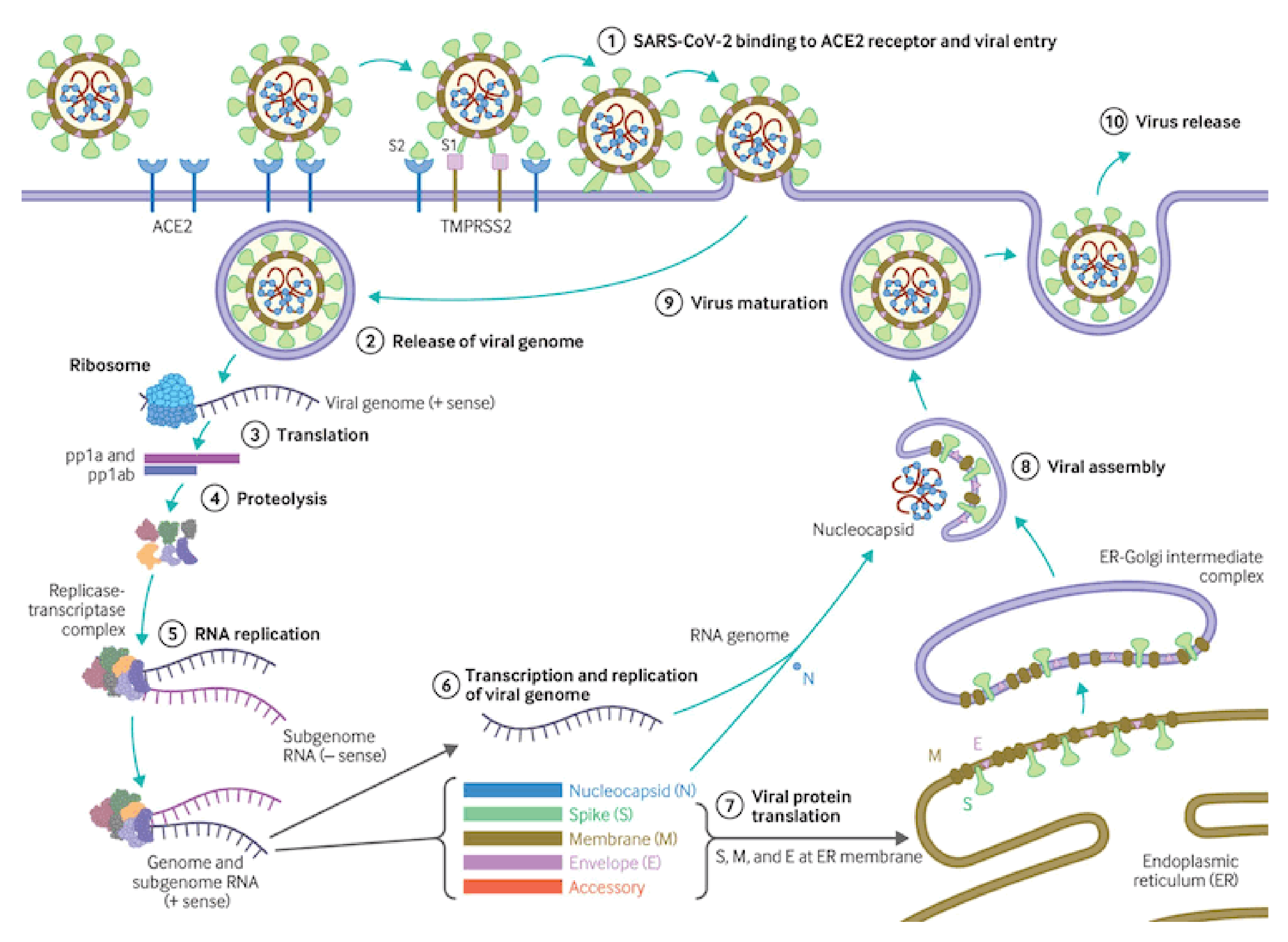

Figure 4: Virus replication cycle

BMJ. 2020;371:m3862

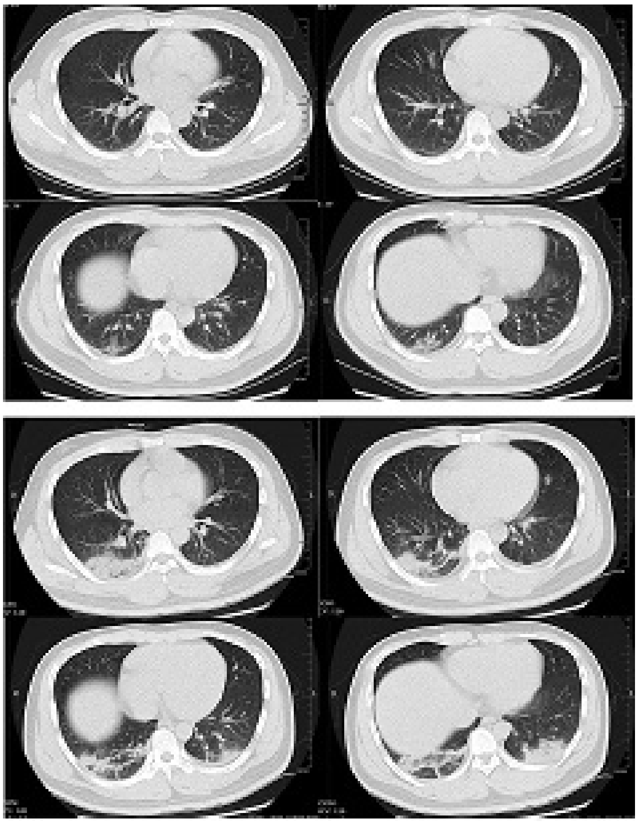

Figure 5: Transverse CT scans from a 32-year-old man, showing ground-glass opacity and consolidation of lower lobe of right lung near the pleura on day 1 after symptom onset (top panel), and bilateral ground-glass opacity and consolidation on day 7 after symptom onset

Xu XW et al. BMJ. 2020;368:m606

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Figure 1 – BMJ Best Practice Numeral Style

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