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Summary

Coronavirus disease 2019 (COVID-19) is an infectious acute respiratory disease caused by a novel coronavirus. The World Health Organization (WHO) was informed of cases of pneumonia of unknown microbial etiology associated with Wuhan City, Hubei Province, China on 31 December 2019. The WHO later announced that a novel coronavirus had been detected in samples taken from these patients. Since then, the epidemic has escalated and rapidly spread around the world, with the WHO first declaring a public health emergency of international concern on 30 January 2020, and then formally declaring it a pandemic on 11 March 2020. Clinical trials and investigations to learn more about the virus, its origin, how it affects humans, and its management are ongoing.

Definition

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

Adults

- In China, 87% of confirmed cases were ages 30 to 79 years and 3% were ages 80 years or older. Approximately 51% of patients were male.[4]
- In Italy, the median age and prevalence of comorbidities was higher compared with China.[5]
- In the UK, the median age of patients was 73 years and males accounted for 60% of admissions in a prospective observational cohort study of more than 20,000 hospitalized patients.[6]
- In the US, older patients (ages ≥65 years) accounted for 31% of all cases, 45% of hospitalizations, 53% of intensive care unit admissions, and 80% of deaths, with the highest incidence of severe outcomes in patients ages ≥85 years.[7] Cases in children, adolescents, and young adults increased between October to December 2020; however, hospitalizations, intensive care unit admissions, and deaths remain low for these groups (2.5%, 0.8%, and <0.1% respectively, based on available data).[8]

Children

- Evidence suggests that children have a lower susceptibility to infection compared with adults, with an odds ratio of 0.56 for being an infected contact compared with adults. Adolescents appear to have similar susceptibility to adults.[9]
- The mean age of children with infection is 6.5 years.[10] Infection rates in children and adolescents vary according to geographic location:[4] [11] [12] [13] [14] [15] [16]
  - China - 2.1% (median age 7 years)
  - Italy - 1.2% (median age 4 to 5 years; higher in males but not statistically significant)
  - Spain - 0.8% (median age 3 years)
  - US - 13.3% (or 4440 cases per 100,000 children in the population) as of 18 March 2021.
- In the UK, a prospective observational cohort study found that children and young adults represented 0.9% of all hospitalized patients at the time. The median age of children admitted to hospital was 4.6 years, 56% were male, 35% were under 12 months of age, and 42% had at least one comorbidity. In terms of ethnicity, 57% were White, 12% were South Asian, and 10% were Black. Age under 1 month, age 10 to 14 years, and Black race were risk factors for admission to critical care.[17]
- In the US, a retrospective cohort study of over 135,000 children found that the mean age of infected children was 8.8 years, and 53% were male. In terms of ethnicity, 59% were White, 15% were Black, 11% were Hispanic, and 3% were Asian. Only 4% of children tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in this population, and clinical manifestations were typically mild.[18]
- Globally, the case fatality rate in children appears to be higher in low- and middle-income countries compared with high-income countries.[19]
- Most cases in children are from familial clusters, or children who have a history of close contact with an infected patient. It is rare for children to be the index case in household transmission clusters.[20] Unlike adults, children do not seem to be at higher risk for severe illness based on age or sex.[21]

Pregnant women
Coronavirus disease 2019 (COVID-19)

• 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. Most studies with a prevalence greater than 15% were from the US, except for two studies from the UK, and one each from Mexico, Turkey, France, and Iran.[22] [23]

• A meta-analysis of over 2500 pregnant women with confirmed COVID-19 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.[24]

• In the UK, the estimated incidence of admission to hospital with confirmed SARS-CoV-2 infection in pregnancy is 4.9 per 1000 maternities. Most women were in the second or third trimester. Of these patients, 41% were ages 35 years or older, 56% were from Black or other ethnic minority groups, 69% were overweight or obese, and 34% had preexisting comorbidities.[25]

• In the US, 78,129 cases have been reported in pregnant women (as of 15 March 2021), with 13,311 hospitalizations and 85 deaths.[26] According to an analysis of approximately 400,000 women ages 15 to 44 years with symptomatic disease, Hispanic and non-Hispanic Black pregnant women appear to be disproportionately affected during pregnancy.[27]

Healthcare workers

• The incidence of infection in healthcare workers ranged from 0% to 49.6% (by polymerase chain reaction), and the prevalence of SARS-CoV-2 seropositivity ranged from 1.6% to 31.6%. The wide ranges are likely related to differences in settings, exposures, rates of community transmission, symptom status, use of infection control measures, and other factors. There was no association between sex and age and risk for infection or seropositivity. However, Black, Asian, or Hispanic ethnicity was significantly associated with an increased risk of infection compared with White people.[28] [29]

• A systematic review and meta-analysis of nearly 130,000 healthcare workers estimated the overall seroprevalence of SARS-CoV-2 antibodies to be 8.7%, with higher seroprevalence reported in North America (12.7%) compared with Europe (8.5%), Africa (8.2%), and Asia (4%). Risk factors for seropositivity included male sex; Black, Asian, or Hispanic ethnicity; working in a COVID-19 unit; patient-facing work; and frontline healthcare work.[30]

• Approximately 14% of the cases reported to the World Health Organization are in healthcare workers (range 2% to 35%).[31]

• The majority of healthcare workers with COVID-19 reported contact in the healthcare setting. In a study of over 9000 cases reported in healthcare workers in the US, 55% had contact only in a healthcare setting, 27% only in a household, 13% only in the community, and 5% in more than one setting.[32]

• The most frequently affected healthcare workers were nurses. Only 5% of healthcare workers developed severe disease and 0.5% died.[33] The incidence of severe or critical disease and mortality in healthcare workers was lower than the incidence of severe or critical disease and mortality in all patients.[34]

• Patient-facing healthcare workers were three times more likely to be admitted to hospital compared with nonpatient-facing workers according to a study in Scotland. In the same study, healthcare workers and their household members accounted for 17% of hospitalizations.[35]

• Analysis of hospitalization data from 13 sites in the US found that 6% of hospitalized adults were healthcare workers, and 36% of these people were in nursing-related roles. Around 90% of hospitalized healthcare workers had at least one underlying condition, the most common conditions being obesity, hypertension, and diabetes.[36]
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.[37]
- 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.[38] [39] The full genome has been determined and published in GenBank. [GenBank] (https://www.ncbi.nlm.nih.gov/genbank/)
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

Emerging SARS-CoV-2 variants

- All viruses, including SARS-CoV-2, change over time. Over 360,000 variants of the virus have been sequenced by the COVID-19 Genomics UK Consortium (COG-UK) as of 23 March 2021. [COG-UK: data] (https://www.cogconsortium.uk/)
- Noteworthy SARS-CoV-2 variants of concern (VOC) include the following.
  - VOC 202012/01 (B.1.1.7 lineage): first identified in Kent, South East of England in September 2020, and reported to the World Health Organization in December 2020. The origin is unclear. It is now the dominant variant in the UK. The variant has been reported in more than 113 countries, and community transmission has been reported in 19 of these countries (as of 8 March 2021). There is evidence that suggests this variant may be more transmissible. Secondary attack rates have been reported to be higher if the index case has this variant. The reported secondary attack rate is 10% in contacts of people without the variant, and 10% to 13% in contacts of people with the variant, across all regions and age groups (based on data from 30 November 2020 to 10 January 2021). Estimated secondary attack rates are 10% to 55% higher than wild-type virus for most regions and age groups.[40] However, secondary attack rates for nonvariant forms are known to vary quite widely (see Secondary attack rate below). There is a possibility that infection with this variant is associated with an increased risk of disease severity, hospitalization, and death compared with other variants.[40] [41] [42] There is consistent evidence of cross-neutralizing activity in convalescent sera (i.e., sera from individuals who have been infected with B1.1.7 shows neutralizing activity against virus from other lineages, and the converse is also true).[40] The variant has mutations that have been associated with attenuation in other variants.[43] There is emerging evidence (yet to peer
The theory reviewed) that the variant may cause longer infections compared with nonvariant SARS-CoV-2, and this may contribute to increased transmissibility.[44]

- **VOC 202102/02 (B.1.1.7 cluster with E484K mutation):** a small number of B.1.1.7 sequences have acquired the spike protein mutation E484K. A small cluster of cases has been reported, mostly in South West England. Only one death has been reported with this variant in the UK. International cases have been reported in two countries (as of 8 March 2021).[40]

- **VOC 202012/02 (B.1.351 lineage):** first detected in Nelson Mandela Bay, South Africa in October 2020. The variant has been reported in at least 62 countries, including the UK (as of 8 March 2021). The variant has similar spike protein mutations to VOC 202012/01. Sequence analysis reveals that the N501Y mutation reported in the UK and South Africa originated independently. These mutations may affect its transmissibility and antigenic profile; however, cases, hospitalizations, and deaths are currently decreasing in South Africa.[40]

- **VOC 202101/02 (P.1 lineage):** a descendant of the B.1.1.28 lineage first detected in Japan in travelers from Brazil. The variant has been reported in at least 20 countries (as of 8 March 2021), including the UK and the US. All cases in the UK have been linked to international travel. Based on modeling and laboratory data, it is plausible that there is some degree of immune escape, or increased transmissibility, or both with this variant. However, the magnitude and clinical significance of these effects are yet to be determined.[40]

- **B.1.427 and B.1.429 lineages:** first detected in California in the US, these variants have been classified as variants of concern by the Centers for Disease Control and Prevention. They have an increased risk of transmission and may not be as responsive to certain treatments.[45]

- **Cluster 5 variant:** detected in people in Denmark and associated with transmission from farmed minks. The clinical implications of this new variant are not yet well understood; however, mutations in the spike protein have been reported. No new human cases of the cluster 5 variant have been reported in Denmark since 20 November 2020, and the variant is no longer circulating in humans. All mink on affected mink farms, and farms within an assigned zone, were culled. Seven other countries have reported SARS-CoV-2 in farmed minks (Lithuania, Greece, Spain, Italy, the Netherlands, Sweden, and the US).[46] [47]

Further investigations are required to more fully understand the impact of these variants. There are many other variants under investigation.

- In a global study of over 12,000 mutations of the SARS-CoV-2 virus (which excluded the variants above), there was no evidence to suggest that any of the identified SARS-CoV-2 variants were associated with increased transmissibility.[48]

### 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.[49] [50] [51] 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.[51]

- Some studies suggest that SARS-CoV-2 may be a recombinant virus between a bat coronavirus and an origin-unknown coronavirus.[38] [39] [52] [53] Pangolins and minks have been suggested as possible intermediate hosts.[54] [55] [56] [57] However, there is currently no evidence to demonstrate the possible route of transmission from a bat reservoir to human through one or several intermediary animal species.[58] Further research is required to determine the origin of SARS-CoV-2.
Transmission dynamics

• Respiratory transmission is the dominant mode of transmission, with proximity and ventilation being the key determinants of transmission risk.[59] Available evidence suggests that transmission between people occurs primarily through direct, indirect, or close contact with infected people through infected secretions such as saliva and respiratory secretions, or through their respiratory droplets, which are expelled when an infected person coughs, sneezes, talks, or sings.[60]

• Airborne transmission can occur in healthcare settings during aerosol-generating procedures. There are also some outbreak reports that suggest aerosol transmission is possible in the community under certain conditions; however, these reports relate to enclosed indoor crowded spaces with poor ventilation where the infected person may have been breathing heavily (e.g., restaurants, choir practice, fitness classes). A detailed investigation of these clusters suggests that droplet and fomite transmission could also explain the transmission in these reports.[60][61] 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.[62]

• 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.[59] The virus has been found to be more stable on plastic and stainless steel (up to 72 hours) compared with copper (up to 4 hours) and cardboard (up to 24 hours) under experimental conditions, but this does not reflect real-life conditions.[63] In healthcare settings, the virus is widely distributed in the air and on object surfaces in both general wards and intensive care units.[64] However, no virus has been cultured from these samples indicating that the deposition may reflect nonviable viral RNA.[65][66][67]

• 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.[59] The pooled detection rate of fecal SARS-CoV-2 RNA in patients with COVID-19 is approximately 51%, with 64% of samples remaining positive for a mean of 12.5 days (up to 33 days maximum) after respiratory samples became negative.[68]

• Transmission via other body fluids (including sexual transmission or bloodborne transmission) has not been reported.[59] While the virus has been detected in blood, cerebrospinal fluid, pericardial fluid, pleural fluid, urine, semen, saliva, ocular tissue including the cornea, tears, and conjunctival secretions, as well as in the middle ear and mastoid, the presence of virus or viral components does not equate with infectivity.[69][70][71][72][73][74][75][76][77][78][79][80][81] SARS-CoV-2 is not sexually transmitted, but may have an effect on male fertility, although this is yet to be confirmed.[82]

• Vertical transmission occurs rarely and transplacental transmission has been documented. There is limited evidence on the extent of vertical transmission and its timing.[83] Overall, 6.3% of infants born to mothers with COVID-19 tested positive for SARS-CoV-2 at birth. Transmission was reported in both preterm and full-term infants. There is also evidence for antibodies against SARS-CoV-2 among infants born to mothers with COVID-19 who tested negative for SARS-CoV-2.[84] The rate of infection appears to be no greater when the baby is born vaginally, breastfed, or allowed contact with the mother.[85] 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. Anti-SARS-CoV-2 antibodies are more prevalent in breast milk compared with viral fragments.[86] Vertical transmission is unlikely to occur if correct hygiene precautions are taken.[87]

• 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.[88] Hospital-acquired infections (defined
as patients diagnosed more than 7 days after hospital admission) accounted for approximately 17% of infections in the NHS England as of 26 October 2020, and rates have been as high as 25% in some areas.[89] 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.[60] [90]

Transmission dynamics in relation to symptoms

- **Symptomatic transmission**
  - Transmission appears to mainly be spread via droplets and close contact with infected symptomatic cases. Transmissibility depends on the amount of viable virus being shed and expelled by a person (viral load is highest just before or around the time of symptom onset and during the first 5-7 days of illness), the type of contact, the setting, and what infection prevention and control measures are in place.[60] [91]

- **Presymptomatic transmission**
  - Transmission may occur during the incubation period, usually 1 to 3 days before symptom onset.[91]
  - Presymptomatic transmission was reported in 12.6% of cases in China, and 6.4% of cases in Singapore.[92] [93]
  - 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).[94] [95] [96] [97] [98] [99] [100] The World Health Organization states that asymptomatic cases are not the major driver of the overall epidemic dynamics.[101] Numerous studies have reported no evidence of asymptomatic transmission from carriers of SARS-CoV-2.[102] [103] [104] In a post-lockdown screening study in nearly 10 million residents in Wuhan, there were no positive tests among 1174 close contacts of asymptomatic cases. In addition to this, virus culture was carried out on samples from asymptomatic positive cases and all cultures were negative, indicating that asymptomatic positive cases in the study were not infectious.[105]
  - Estimating the prevalence of asymptomatic cases in the population is difficult. A meta-analysis of over 50,000 people found that 15.6% of confirmed cases were asymptomatic at the time of testing (range 2% to 75%), and nearly half developed symptoms later.[106] The overall estimate of the proportion of people who become infected and remain asymptomatic throughout infection has been estimated to be 17% to 33%.[107] [108] [109] [110]
  - 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.[111] A cross-sectional study of nearly 2800 healthcare workers found that 5.4% of COVID-19-facing asymptomatic healthcare workers tested positive, compared with 0.6% of non-COVID-19-facing asymptomatic healthcare workers.[112]
  - Children are more likely to be asymptomatic.[106] The pooled proportion of asymptomatic cases in children was thought to be significant (around 40%).[113] [114] However, recent studies have
found that the rate of asymptomatic infection in children was very low (1% compared with 9% in adults in one study, and 0.6% compared with 1.8% in adults in another study), indicating that children appear not to be particular drivers of the pandemic.[115] [116]

Superspreading events

• Superspreading events have been reported. These events are associated with explosive growth early in an outbreak and sustained transmission in later stages.[117]
• Reported events include church/religious gatherings, family or social gatherings, weddings, choir practices, overnight youth camps or high school retreats, fitness classes, indoor recreational sporting activities, business conferences, and working in call centers.[59] [118] [119] [120] [121] Widespread transmission has also been reported in long-term care facilities, homeless shelters, prisons, immigration detention centers, and meat and poultry processing facilities, as well as on board cruise ships.[122] [123] [124] [125] [126] [127] [128] [129] [130]
• Limited transmission has been reported in childcare, school, and university settings, and infected cases may transmit the infection to their household members.[131] [132] [133] There is limited high-quality evidence to quantify the extent of transmission in schools, or to compare it with community transmission. However, emerging evidence suggests a lower overall infection attack rate in students (0.15%) compared with school staff (0.7%).[134]
• 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.[135]

Viral transmission factors

• Incubation period
  • The incubation period is estimated to be between 1 and 14 days, with a median of 5 to 7 days.[136] [137] Viable virus is relatively short lived; infectiousness peaks around 1 day before symptom onset and declines within 7 days.[59]
  • The pooled mean incubation period is 9.6 days in children.[10]
• Reproduction number (R₀)
  • Reports suggest that the reproduction number, the number of people who acquire the infection from an infected person, is estimated to be 2.2 to 3.3. However, there is very high heterogeneity across studies and the number varies between countries.[51] [138] [139] [140] The Centers for Disease Control and Prevention gives a current best estimate of 2.5 (as of 19 March 2021).[141]
  • The R₀ decreases when public health measures (e.g., social distancing) are put in place.[142]
• Serial interval
  • The time between the start of symptoms in the primary patient and the onset of symptoms in the patient being infected in a chain of transmission has been estimated to be approximately 5.45 days (range 4.2 to 6.7 days).[143]
• Secondary attack rate
  • The secondary attack rate is the proportion of people exposed to an index (or primary) case that go on to develop the disease as a result of the exposure.
• The pooled secondary attack rate among all close contacts of an index case has been estimated to be 7%.[144]

• The secondary attack rate differs between contact settings. More familiar prolonged contact increases the potential for transmission. Pooled estimates of the secondary attack rate range from 1.2% to 5.9% in social settings (depending on level of contact and whether contact is with strangers or family and friends), 1.9% in workplaces (based on limited data), 3.6% in healthcare facilities, and 21.1% for household settings (increases with exposure >5 days).[145]

• Another systematic review and meta-analysis of household transmission estimates the pooled household secondary attack rate to be slightly lower at 16.6%. The rate is higher for symptomatic index cases (18%) compared with asymptomatic cases (0.7%), and adults have a higher susceptibility to infection compared with children. Spouses of the index case are more likely to be infected compared with other household members.[146]

• The secondary attack rate increases with the severity of the index case (i.e., 0.3% for asymptomatic cases to 6.2% for severe/critical cases) according to a study of 3410 close contacts of 391 index cases.[101]

• The secondary attack rate for close contacts of presymptomatic people has been estimated to be approximately 7%, compared with 1% in asymptomatic people and 6% in symptomatic people.[147]

• Children ages <5 years had lower secondary attack rates compared with older children, and the risk of infection was higher if the household index case was the mother.[148] The secondary attack rate was 1.2% in children in a childcare setting or school.[149]

• Secondary attack rates for SARS-CoV-2 variants may differ (see Emerging SARS-CoV-2 variants above).

• Viral load

• 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.[150]

• Viral load appears to be a leading driver of virus transmission. In one cohort study, the secondary attack rate was 17% among 753 contacts of index cases, with a variation from 12% when the index case had a viral load lower than 1x10⁶ copies/mL to 24% when the index case had a viral load of 1x10¹⁰ copies/mL or higher (in nasopharyngeal swabs). Higher viral loads in swabs of asymptomatic contacts were associated with a higher risk of developing symptomatic disease, and these contacts had shorter incubation periods than those with a lower viral load.[151]

• Viral shedding

• The mean duration of shedding was 17 days in the upper respiratory tract, 14.6 days in the lower respiratory tract, 17.2 days in stool, and 16.6 days in serum samples. The maximum duration of shedding was 83 days in the upper respiratory tract, 59 days in the lower respiratory tract, 126 days in stool, and 60 days in serum samples. However, no live virus was detected beyond day 9 of symptoms, despite persistently high viral loads. Duration of viral shedding
was longer in symptomatic patients compared with asymptomatic patients, and in patients with severe illness compared with those with nonsevere illness.[150]

- The period of infectiousness is far shorter than the duration of detectable viral shedding. 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. Data about the dynamics of viral shedding in people with persistent asymptomatic infection are inconsistent.[59] There is no convincing evidence that duration of viral shedding correlates with duration of infectivity.[152]

- Factors associated with prolonged viral shedding include male sex, older age, comorbid hypertension, delayed admission to hospital after symptom onset or severe illness on admission, and use of invasive mechanical ventilation or corticosteroids.[153] Immunocompromised patients may shed for at least 2 months.[154]

Pathophysiology

The pathophysiology is not yet fully understood; however, details are emerging.[155]
• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the ACE2 receptor in humans, which suggests a similar pathogenesis to SARS.[39][156]

• A unique structural feature of the spike glycoprotein receptor-binding domain of SARS-CoV-2 (which is responsible for the entry of the virus into host cells) confers potentially higher binding affinity for ACE2 on host cells compared with SARS-CoV-1.[157] This furin-like cleavage site does not exist in other SARS-like coronaviruses.[158] The binding energy between the SARS-CoV-2 spike protein and ACE2 was highest for humans out of all species tested, suggesting that the SARS-CoV-2 spike protein is uniquely evolved to bind to and infect human cells expressing ACE2.[159]

• Mechanistic evidence from other coronaviruses suggests that SARS-CoV-2 may downregulate ACE2, leading to a toxic overaccumulation of plasma angiotensin-II, which may induce acute respiratory distress syndrome and fulminant myocarditis.[160][161]

• Based on an analysis of single-cell RNA sequencing datasets derived from major human physiologic systems, the organs considered more vulnerable to SARS-CoV-2 infection due to their ACE2 expression levels include the lungs, heart, esophagus, kidneys, bladder, and ileum.[162] This may explain the extrapulmonary manifestations associated with infection. ACE2 expression has also been identified in the diaphragm, which may lead to diaphragm fibrosis and myopathy.[163]

• Lower expression of ACE2 in the nasal epithelium of children ages <10 years compared with adults may explain why COVID-19 is less prevalent in children; however, further research on this is required.[164]

Transmembrane protease serine 2 (TMPRSS2)

• SARS-CoV-2 uses host TMPRSS2 for S protein priming and fusion of viral and host cell membranes.[165]

• Higher expression of TMPRSS2 has been noted in the nasal epithelium of Black people compared with Asian people, Latin people, White people, and people of mixed race/ethnicity, which may be a contributing factor to the higher burden of infection among Black people.[166]

Autopsy studies

• Pulmonary: autopsy studies have revealed that patients who died of respiratory failure had evidence of exudative diffuse alveolar damage with massive capillary congestion, often accompanied by microthrombi. Hyaline membrane formation and pneumocyte atypical hyperplasia are common. Pulmonary artery obstruction by thrombotic material at both the macroscopic and microscopic levels has been identified. Patients also had signs of generalized thrombotic microangiopathy. Severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes has been noted. Other findings include bronchopneumonia, pulmonary embolism, alveolar hemorrhage, and vasculitis. Significant new blood vessel growth through intussusceptive angiogenesis distinguishes the pulmonary pathology of COVID-19 from severe influenza infection.[167][168][169][170][171][172] Some patients with severe disease may develop fibrotic lung disease for which lung transplantation may be the only treatment option.[173]

• Neurologic: histopathologic examination of brain specimens showed hypoxic changes but no encephalitis or other specific brain changes due to the virus in one autopsy study. The virus was detected at low levels in brain tissue.[174] Another study found mild neuropathologic changes, with pronounced neuroinflammatory changes in the brainstem being the most common finding.[175]

• Cardiac: SARS-CoV-2 has been frequently detected in the myocardium in autopsy studies. While cardiac pathologic findings are prevalent, acute myocarditis is uncommon. The most frequent findings were cardiac dilatation, myocardial ischemia, and thrombosis.[176] The virus, along with inflammatory
Coronavirus disease 2019 (COVID-19) theory

Changes, has been reported in the cardiac tissue of a child with pediatric inflammatory multisystem syndrome.[177]

- Immunology: the mechanisms contributing to increased thrombosis involve extensive cross-talk between the immune system and hemostasis.[178] Evaluation of immune infiltrate has revealed a notable presence of aggregated neutrophils in the lungs and several other organs. Neutrophilic plugs, composed of neutrophils with neutrophil extracellular traps (NETs) or as aggregates of NETs and platelets, were present in the heart, kidney, liver, and brain. NETs may therefore play a role in coagulopathy associated with SARS-CoV-2 infection. The disproportionate presence of aggregate neutrophils and NETs in comparison with the sporadic presence of virus suggests an autonomous maladaptive immune response.[179] NETs appear to play a role in the pathogenesis of ST-elevation myocardial infarction in COVID-19 patients based on a small case series of patients with COVID-19 and myocardial infarction.[180]

- Hepatic: a high prevalence of hepatic steatosis, congestion of hepatic sinuses, vascular thrombosis, and fibrosis have been noted, along with portal and lobular inflammation and Kupffer cell hyperplasia or proliferation.[181]

- Other: other novel findings at autopsy include pancreatitis, pericarditis, adrenal microinfarction, secondary disseminated mucormycosis, and brain microglial activation.[182]

Endothelial dysfunction

- There is a hypothesis that COVID-19 is a disease of the endothelium.[183] [184] [185] Endotheliopathy and platelet activation appear to be important features of COVID-19 in hospitalized patients and are likely to be associated with coagulopathy, critical illness, and death.[186]

- Hyperviscosity has been reported in patients. It is known to damage the endothelium, and is a known risk factor for thrombosis. The potential link between hyperviscosity and thrombotic complications warrants further investigation.[187]

Genetic factors

- Genetic factors are thought to play a role. In a case series of four male patients with severe disease, rare putative loss-of-function variants of X-chromosomal TLR7 were identified, and this was associated with impairment of interferon responses.[188]

- A novel susceptibility locus has been detected at a chromosome 3p21.31 gene cluster in patients with respiratory failure, which may confirm the involvement of the ABO blood-group system.[189]

Classification


Mild illness

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

- Common symptoms include fever, cough, fatigue, anorexia, dyspnea, and myalgia. Other nonspecific symptoms include sore throat, nasal congestion, headache, diarrhea, nausea/vomiting, and loss of smell/taste. Additional neurologic manifestations reported include dizziness, agitation, weakness, seizures, or findings suggestive of stroke. Children may not report fever or cough as frequently as adults.
- Older people and immunosuppressed people may present with atypical symptoms (e.g., fatigue, reduced alertness, reduced mobility, diarrhea, loss of appetite, delirium, absence of fever).
- Symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events (e.g., dyspnea, fever, gastrointestinal symptoms, fatigue) or other diseases (e.g., malaria) may overlap with COVID-19 symptoms.

Moderate disease

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

Severe disease

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

Critical disease

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

National Institutes of Health: clinical classification of COVID-19[3]

Asymptomatic or presymptomatic infection
Coronavirus disease 2019 (COVID-19)

**Theory**

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

**Mild illness**

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

**Moderate illness**

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

**Severe illness**

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

**Critical illness**

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

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

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

**Case 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) the next day. The patient is started on dexamethasone.

**Case history #2**

A 26-year-old woman presents at her local COVID-19 testing clinic with symptoms of a sore throat and loss of taste. She denies having a fever, and has not knowingly been in contact with a confirmed case of COVID-19. After being tested, she is advised to go home, self-isolate until her test results are sent to her
Coronavirus disease 2019 (COVID-19)

via text message, and call her doctor if her symptoms get worse. She receives a text message later that day confirming that her test is positive for SARS-CoV-2, and that she must self-isolate according to her local public health recommendations.

Other presentations

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

COVID-19 is a notifiable disease. Report all suspected or confirmed cases to your local health authorities.

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.

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. Suspected cases should remain in the pathway until proven negative. Immediately isolate all suspected and confirmed cases and implement local infection prevention and control procedures. Triage patients with a standardized triage tool and evaluate the patient to assess the severity of disease. Use clinical judgment, including consideration of the patient’s values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the intensive care unit, rather than currently available prediction models for prognosis.[136]

Best Practice has published a separate topic on the management of coexisting conditions in the context of COVID-19. [BMJ Best Practice: Management of coexisting conditions in the context of COVID-19] (https://bestpractice.bmj.com/topics/en-us/3000190#important-update)

Key recommendations

- Isolate all suspected or confirmed cases immediately. Triage patients with a standardized triage tool and evaluate the severity of disease. Follow local infection prevention and control guidelines.[136]
- Have a high index of clinical suspicion in all patients who present with fever and/or acute respiratory illness. People with a history of residence/work/travel in a location with a high risk of transmission or community transmission and contacts of probable and confirmed cases are at higher risk of infection.[190]
- Suspect the diagnosis in patients with a new continuous cough, fever, or altered sense of taste or smell.[442] Patients may also present with symptoms including dyspnea, fatigue, myalgia/arthralgia, sore throat, headache, nasal congestion or rhinorrhea, sputum production, chest tightness, or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).[443]
- Order a real-time reverse transcription polymerase chain reaction (RT-PCR) to confirm the diagnosis. Upper and lower respiratory specimens are preferred. Serologic testing may be useful in some settings.[444] Results should be interpreted in the context of the pretest probability of disease.
- Be on high alert for children and adolescents with acute gastrointestinal symptoms and signs of cardiac inflammation. Evidence so far suggests a milder or asymptomatic course of disease in children.[445] However, a rare multisystem inflammatory condition with some features similar to those of Kawasaki disease and toxic shock syndrome has been temporally associated with COVID-19 in children and adolescents.[446]
- Order the following laboratory investigations in hospitalized patients: complete blood count, comprehensive metabolic panel, arterial blood gas, blood glucose level, coagulation screen, inflammatory markers, cardiac biomarkers, serum creatine kinase, and blood and sputum cultures for other pathogens. Pulse oximetry may reveal low oxygen saturation.
Coronavirus disease 2019 (COVID-19)

Diagnosis

• 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. Consult local guidelines.
• For full details and guidance see information below.

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:

• People residing or working in an area with a high risk of transmission (e.g., closed residential settings, humanitarian setting), people residing in or traveling to an area with community transmission, and people working in a health setting (including within health facilities and households) at any time within the 14 days prior to symptom onset
• People who have had contact with a probable or confirmed case. A contact is a person who has experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:
  • Face-to-face contact with a probable or confirmed case within 3 feet (1 meter) and for at least 15 minutes
  • Direct physical contact with a probable or confirmed case
  • Direct care for a patient with probable or confirmed COVID-19 without using recommended personal protective equipment
  • Other situations as indicated by local risk assessments.

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

Ask anyone seeking routine or emergency care, regardless of whether they have symptoms, about recent travel to countries where there is transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (consult local guidance for current list of countries), or whether they are a contact of a returning traveler from these countries.

Clinical presentation in adults

Approximately 15% of patients present with the symptom triad of fever, cough, and dyspnea, and 90% present with more than one symptom. 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. According to a UK study, approximately 25% of people who had evidence of past infection were asymptomatic, and 40% did not have one of the three classic symptoms (i.e., fever, persistent dry cough, altered sense of taste/smell).

The most common symptoms are:

• Fever
• Cough
Coronavirus disease 2019 (COVID-19)

Diagnosis

- Dyspnea
- Altered sense of taste/smell.

Less common symptoms include:

- Myalgia or arthralgia
- Fatigue
- Sputum production
- Chest tightness
- Gastrointestinal symptoms
- Sore throat
- Headache
- Dizziness
- Neurologic symptoms
- Ocular symptoms
- Audio-vestibular symptoms
- Cutaneous symptoms
- Rhinorrhea/nasal congestion
- Chest pain
- Hemoptysis.

Signs and symptoms of febrile respiratory illness may not possess the necessary sensitivity for early diagnostic suspicion. A Cochrane review found that at least half of patients had a cough, sore throat, fever, myalgia/arthralgia, fatigue, or headache. Anosmia and/or ageusia was also common. The presence of fever, myalgia/arthralgia, fatigue, and headache substantially increased the likelihood of COVID-19 when present. Cough and sore throat were common in people without COVID-19, so these symptoms alone were less helpful for diagnosis. No single symptom or sign included in the review could accurately diagnose COVID-19 and the authors concluded that neither the absence or presence of signs or symptoms are accurate enough to rule in or rule out disease. However, the presence of anosmia and/or ageusia may be useful as a red flag for diagnosis. The presence of fever or cough may also be useful to identify people for further testing. Nonrespiratory symptoms may appear before the onset of fever and lower respiratory tract symptoms. Lower urinary tract symptoms have also been reported rarely.

Preliminary data from the Office for National Statistics in the UK suggest that people infected with the VOC 202012/01 (B.1.1.7 lineage) variant are more likely to have cough, sore throat, fatigue, and myalgia, and are less likely to have altered sense of taste/smell, compared with those infected with other variants. However, analysis of symptom data by researchers at King’s College London found no significant differences in symptoms, severity, or duration of disease caused by the new variant.

The clinical presentation has varied slightly across geographic locations. Initial impressions from the US note that the clinical presentation may be broader than that observed in China and Italy, with chest pain, headaches, altered mental status, and gastrointestinal symptoms all observed on initial presentation. Severe hepatic and renal dysfunction that spares the lungs has also been observed. Data from the first hospitalized patients in New York found that while the most common presenting symptoms were fever, cough, dyspnea, and myalgia, gastrointestinal symptoms appeared to be more common than in China.

Severity

- 80% of adults present with mild to moderate illness
• 14% of adults present with severe illness
• 5% of adults present with critical illness
• 1% of adults present with asymptomatic illness.[4]

The most prevalent symptoms in patients with mild to moderate illness, according to one European study, are headache, loss of smell, nasal congestion, cough, asthenia, myalgia, rhinorrhea, gustatory dysfunction, and sore throat. Fever was reported less commonly. The mean duration of symptoms was 11.5 days. The presentation varied according to age, with younger patients generally having ear, nose, and throat complaints, and older patients generally having fever, fatigue, and loss of appetite.[455] More common symptoms in patients with severe disease include fever, dyspnea, and anorexia.[139]

Pregnant women

• The clinical characteristics in pregnant women are similar to those reported for nonpregnant adults.[456] 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.[22] [23]
• 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.[136]

Atypical presentations

• Atypical presentations may occur, especially in older patients and patients who are immunocompromised (e.g., falls, delirium/confusion, functional decline, reduced mobility, syncope, persistent hiccups, absence of fever). Older patients and those with comorbidities may present with mild symptoms, but have a high risk of deterioration.[136]
• There have been case reports of parotitis (possibly related to intraparotid lymphadenitis), oral vesiculobullous lesions, retinal lesions, and androgenetic alopecia in patients with COVID-19; however, it is unknown whether these findings are associated with SARS-CoV-2 infection as yet.[457] [458] [459] [460]

Coinfections

• The pooled prevalence of coinfection with viruses and atypical bacteria in SARS-CoV-2-positive patients was 11.6% (16.8% in studies that tested 100% of patients for copathogens).[461]
• Bacterial coinfections have been reported in 7% of hospitalized patients, and 14% of patients in intensive care units. The most common bacteria were *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Klebsiella pneumoniae*. Coinfections with fungal pathogens and viruses (e.g., respiratory syncytial virus, influenza A) were less commonly reported.[462]
• Fungal infections have been reported in 12% of patients admitted to the intensive care unit.[463]
• Coinfections are more common in critically ill patients.[464]
• Coinfections may be associated with protracted respiratory symptoms, prolonged intensive care stay, morbidity, and mortality if not detected and treated early.[465]
• Patients with influenza coinfection showed similar clinical characteristics to patients with COVID-19 only.[466] [467]
• Patients with tuberculosis or influenza and SARS-CoV-2 coinfection have an increased risk of mortality, while the clinical outcomes in patients with HIV or chronic hepatitis and SARS-CoV-2 coinfection are comparable to patients without coinfection.[468]

Clinical presentation in children

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

Evidence suggests a milder, or asymptomatic, disease course in the majority of children, with low rates of severe disease and mortality. Infants under 1 year of age and adolescents 10 to 14 years of age have a higher risk for developing severe disease. Risk factors for severe disease include the presence of comorbidities and higher viral load. The clinical presentation in children is heterogeneous and includes a wide spectrum of clinical features. The most common presenting symptoms in children are fever and cough. Gastrointestinal symptoms (nausea, vomiting, diarrhea) are also common in children. Other less common symptoms include dyspnea, nasal congestion, rhinorrhea, rash, conjunctivitis, fatigue, abdominal pain, and neurologic symptoms. A higher prevalence of gastrointestinal symptoms has been reported in children >5 years of age compared with children ≤5 years of age.[445] Fever, cough, appetite loss, and dyspnea are less common in children compared with adults.[469]

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.[445] [470] [471] [472]

Be alert for signs and symptoms of pediatric inflammatory multisystem syndrome (PIMS), also known as multisystem inflammatory syndrome in children (MIS-C). Consider PIMS/MIS-C in children presenting with fever and abdominal symptoms, particularly if they develop conjunctivitis or a rash. Refer to a pediatric emergency department for evaluation.[473] See the Complications section for more information.

Coinfections may be more common in children.[474] Coinfection was documented in 6% of children in US and Italian studies, with the most common pathogens being respiratory syncytial virus, rhinoviruses, Epstein-Barr virus, enteroviruses, influenza A, non-SARS coronaviruses, and Streptococcus pneumoniae.[12] [475]

Physical exam

Perform a physical exam. Avoid use of a stethoscope if possible due to risk of viral contamination. 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. 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.[476]

Pulse oximetry

Pulse oximetry may reveal low oxygen saturation (SpO₂ <90%). 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.[477]
The UK National Institute for Health and Care Excellence recommends using oxygen saturation levels below 94% for adults (or below 88% for adults with known type 2 respiratory failure) and below 91% for children in room air at rest to identify people who are seriously ill.[478]

Pulse oximeters may exhibit suboptimal accuracy in certain populations. Limited data from studies with small numbers of participants suggest that skin pigmentation can affect pulse oximeter accuracy. In one study, occult hypoxemia (defined in the study as arterial oxygen saturation <88% by arterial blood gas despite oxygen saturation of 92% to 96% on pulse oximetry) was not detected by pulse oximetry nearly three times more frequently in Black patients compared with White patients.[479] The US Food and Drug Administration (FDA) has warned that multiple factors can affect the accuracy of a pulse oximeter reading (e.g., poor circulation, skin pigmentation, skin thickness, skin temperature, current tobacco use, use of fingernail polish). The FDA recommends considering accuracy limitations when using a pulse oximeter to assist in diagnosis and treatment decisions, and to use trends in readings over time rather than absolute cut-offs if possible.[480]

Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognizing further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[477]

While NEWS2 is still recommended for use in patients with COVID-19, the UK Royal College of Physicians now advises that any increase in oxygen requirements in these patients should trigger an escalation call to a competent clinical decision maker, and prompt an initial increase in observations to at least hourly until a clinical review happens.[481]

Initial laboratory investigations

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

- ABG
- CBC
- Comprehensive metabolic panel
- Blood glucose level
- Coagulation screen
- Inflammatory markers (e.g., serum C-reactive protein, erythrocyte sedimentation rate, interleukin-6, lactate dehydrogenase, procalcitonin, amyloid A, and ferritin)
- Cardiac biomarkers
- Serum creatine kinase and myoglobin.

The most common laboratory abnormalities are lymphopenia, leukocytosis, leukopenia, thrombocytopenia, hypoalbuminemia, elevated cardiac biomarkers, elevated inflammatory markers, elevated D-dimer, and abnormal liver and renal function.[454] [482] [483] [484] 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]

Collect blood and sputum specimens for culture in patients with severe or critical disease to rule out other causes of lower respiratory tract infection and sepsis, especially patients with an atypical epidemiologic history. Specimens should be collected prior to starting empiric antimicrobials if possible.[136]
Molecular testing

Testing strategies vary widely between countries.[488]

Molecular testing is required to confirm the diagnosis. Molecular testing is an aid to diagnosis only. The World Health Organization (WHO) recommends that healthcare providers consider a positive or negative result in combination with specimen type, clinical observations, patient history, and epidemiologic information. Where a test result does not correspond with the clinical presentation, a new specimen should be taken and retested using the same or a different molecular test (see Limitations of molecular testing below).[489]

Order a nucleic acid amplification test, such as real-time reverse-transcription polymerase chain reaction (RT-PCR), for SARS-CoV-2 in patients with suspected infection whenever possible (see the Criteria section).[444] 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 of concern.[192]

Who to test

- Base decisions about who to test on clinical and epidemiologic factors.[444]
- In the UK, testing is recommended in:[490]
  - People with symptoms of new continuous cough, high temperature, or altered sense of smell/taste
  - People with acute respiratory infection, influenza-like illness, clinical or radiologic evidence of pneumonia, or acute worsening of underlying respiratory illness, or fever without another cause (whether presenting in primary or secondary care).
- In the US, testing is recommended in:[491]
  - People with symptoms, even if they are mild
  - People who are asymptomatic and have been in close contact (less than 6 feet [2 meters] for a total of 15 minutes or more over a 24-hour period) with a person with documented infection
  - People who are asymptomatic and have not been in close contact with a person with documented infection only if required by a healthcare provider or public health official.
- The American Academy of Pediatrics recommends testing children with symptoms consistent with COVID-19, children in close contact with an individual with probable or confirmed infection, and children who require screening based on recommendations from public health authorities or other situations (e.g., prior to a medical procedure such as elective surgery or as a school or workplace requirement). The decision to test does not differ by the age of the child. Testing is not recommended for other illnesses that lack shared symptoms (e.g., urinary tract infection, cellulitis), or for children exposed to close contacts of infected individuals unless those contacts are symptomatic or other criteria are met.[492]
- Consult local health authorities for guidance as testing priorities depend on local recommendations and available resources.

Specimens
• The optimal specimen for testing depends on the clinical presentation and the time since symptom onset. The WHO recommends the following.[444]

• 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 naso/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: 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.[493] [494] [495] [496] The WHO does not currently recommend the use of saliva as the sole specimen type for routine clinical diagnostics. In contrast, the Infectious Diseases Society of America recommends saliva as a suitable option for molecular testing in symptomatic people.[497]

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

• Recommended specimen types may differ between countries. For example, in the US, the Centers for Disease Control and Prevention (CDC) recommends the following upper respiratory specimens: nasopharyngeal or oropharyngeal swab; nasal mid-turbinate swab; anterior nares swab; or nasopharyngeal/nasal wash/aspirate. Recommended lower respiratory tract specimens include: sputum, bronchoalveolar lavage, tracheal aspirate, pleural fluid, and lung biopsy.[498] Nasal mid-turbinate swab is an acceptable specimen for home or onsite self-collection.[498]

• Collect specimens under appropriate infection prevention and control procedures.

Test result

• A positive RT-PCR result confirms SARS-CoV-2 infection (in the context of the limitations associated with RT-PCR testing). If the result is negative, and there is still a clinical suspicion of infection (e.g., an epidemiologic link, typical x-ray findings, absence of another etiology), resample the patient and repeat the test. A positive result confirms infection. If the second test is negative, consider serologic testing (see below).[444]

• 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.[444]

Complications of nasal swab testing

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Coronavirus disease 2019 (COVID-19)

**Diagnosis**

- Complications associated with nasal swab testing are not well characterized. Adverse effects may include epistaxis, nasal discomfort, headache, ear discomfort, and rhinorrhea.[499]
- A case of iatrogenic cerebrospinal fluid leak has been reported after nasal testing for COVID-19 in a woman with an undiagnosed skull base defect at the fovea ethmoidalis.[500]

**Testing for other infections**

- Collect nasopharyngeal swabs for testing to rule out infection with other respiratory pathogens (e.g., influenza, atypical pathogens) when clinically indicated according to local guidance. Depending on local epidemiology and clinical symptoms, test for other potential causes including malaria, dengue fever, and typhoid fever as appropriate. It is important to note that coinfections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19.[136] [501]
- When SARS-CoV-2 and influenza viruses are cocirculating, test for both viruses in all hospitalized patients with acute respiratory illness, and only test for influenza virus in outpatients with acute respiratory illness if the results will change clinical management of the patient.[439]

**Limitations of molecular testing**

Molecular testing is an aid to diagnosis only. The WHO recommends that healthcare providers consider a positive or negative result in combination with specimen type, clinical observations, patient history, and epidemiologic information. It also recommends that laboratories ensure that specimens with high cycle threshold values are not incorrectly assigned a positive result due to background noise, and that they provide the cycle threshold value in the report to the healthcare provider. Disease prevalence alters the predictive value of test results. As disease prevalence decreases, the risk of a false positive increases. This means that the probability that a person who has a positive result is truly infected decreases as prevalence decreases, irrespective of the claimed specificity of the test. Careful interpretation of weak positive results is needed.[489]

**Interpret RT-PCR test results with caution.**

- The evidence for the use of RT-PCR in the diagnosis of COVID-19 is still emerging, and uncertainties about its efficacy and accuracy remain. Estimates of diagnostic accuracy need to be interpreted with caution in the absence of a definitive reference standard to diagnose or rule out COVID-19. Also, more evidence is needed about the efficacy of testing outside of hospital settings and in asymptomatic or mild cases.[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 gold standard test against which any diagnostic index test for viruses must be measured and calibrated, to understand the predictive properties of that test.[503] 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.[504]
- As there is no clear-cut "gold standard" for COVID-19 testing, evaluating test results can be challenging. Clinical adjudication may be the best available ‘gold standard’ based on repeat swabs, history, clinical presentation, and chest imaging.[505]

It is not clear whether a positive result always indicates the presence of infectious virus.
- RT-PCR detects viral RNA, but it is not fully understood how that represents infectious virus. Complete live viruses are necessary for transmission, not the fragments identified by PCR.\[506\] 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.\[503\]
- 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.\[507\] Another study found that patients with a cycle threshold of 34 or above do not excrete infectious virus.\[508\] 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.\[506\]
- [Centre for Evidence-Based Medicine: are you infectious if you have a positive PCR test result for COVID-19?](https://www.cebm.net/covid-19/infectious-positive-pcr-test-result-covid-19/)

Interpreting test results depends on the accuracy of the test itself, and the pre- and post-test probabilities of disease. The accuracy of the result depends on various factors including the site and quality of sampling, stage of disease, degree of viral multiplication or clearance, and disease prevalence.\[505\]

- 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.\[505\] When the pretest probability is low, positive results should be interpreted with caution, and ideally a second specimen tested for confirmation.\[509\]
- Post-test probability: the lower the prevalence of disease in a given population, the lower the post-test probability.\[510\] 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.\[511\]
- [BMJ Practice Pointer: interpreting a covid-19 tests result](https://www.bmj.com/content/369/bmj.m1808)

False-positive results

- False-positive results can be caused by a laboratory error or a cross-reaction with antibodies formed by current and past exposure to seasonal human coronavirus infections (e.g., common cold).\[512\] False-positive results are more likely when the prevalence of SARS- CoV-2 is moderate to low.\[513\]
- 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%.\[514\] 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.[509]

• Examples of the potential consequences of false-positive test results include:[509]
  • 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 results

• False-negative rates of between 2% and 29% have been reported.[505] 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.[515]

• 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.[516]

• Examples of the potential consequences of false-negative test results include:[505]
  • Patients may be moved into non-COVID-19 wards leading to spread of hospital-acquired infection
  • Caregivers could spread infection to vulnerable dependents
  • Healthcare workers risk spreading the infection to multiple vulnerable individuals.

Serologic testing

Serology cannot be used as a standalone diagnostic test for acute SARS-CoV-2 infections. However, it may be useful in various settings (e.g., negative molecular testing, diagnosing patients with late presentation or prolonged symptoms, serosurveillance studies).[444] [517]

[BMJ practice pointer: testing for SARS-CoV-2 antibodies] (https://www.bmj.com/content/370/bmj.m3325)

The WHO recommends collecting a paired serum sample, one specimen in the acute phase and one in the convalescent phase 2 to 4 weeks later, in patients where infection is strongly suspected and the RT-PCR result is negative.[444]

• 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.

The CDC recommends serologic testing as a method to support the diagnosis of acute infection in patients who present late (i.e., 9 to 14 days after symptom onset) in addition to other viral detection methods (e.g., RT-PCR, antigen detection tests), or patients who present with late complications (e.g., pediatric inflammatory multisystem syndrome in children).[518]
• Assays with FDA emergency-use authorization are preferred. There is no advantage of assays whether they test for immunoglobulin G (IgG), IgM and IgG, or total antibody.
• The test’s positive predictive value should be optimized by choosing tests with high specificity (e.g., >99.5%) and testing people or populations with a high pretest probability of having antibodies, or using an orthogonal testing algorithm. Results should be interpreted in the context of the expected predictive values (positive and negative).

The Infectious Diseases Society of America recommends serologic testing in the following circumstances:[519]

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

Antibody responses to SARS-CoV-2 typically occur during the first 1 to 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.[520] [521]

A Cochrane review found that antibody tests for IgG/IgM only detected 30% of people with COVID-19 when the test was performed 1 week after the onset of symptoms, but accuracy increased in week 2 with 70% detected and week 3 with over 90% detected. Data beyond 3 weeks were limited. Tests gave false-positive results in 2% of patients without COVID-19. The review found that the sensitivity of antibody tests is too low in the first week since symptom onset to have a primary role in the diagnosis of COVID-19, but tests are likely to have a useful role in detecting previous infection if used 15 or more days after symptom onset (although there were very little data beyond 35 days).[522]

Limitations of serologic testing

The evidence for the use of antibody tests in the diagnosis of COVID-19 is still emerging, and uncertainties about their efficacy and accuracy remain. Estimates of diagnostic accuracy need to be interpreted with caution in the absence of a definitive reference standard to diagnose or rule out COVID-19. More evidence is needed about the efficacy of testing outside of hospital settings and in asymptomatic or mild cases. The estimated sensitivity of antibody tests ranged from 18.4% to 96.1% (the lowest reported sensitivity was from a point-of-care test, although a sensitivity <50% was reported for one laboratory test), and specificity ranged from 88.9% to 100%.[502]

Understanding of the antibody response to SARS-CoV-2 is still emerging; therefore, antibody detection tests must be used with caution, and not used to determine acute infections.[444]

• Results do not indicate the presence or absence of current or previous infection with certainty as IgM and IgG antibodies may take 1 to 3 weeks to develop after infection.[518] A reliable diagnosis is often only possible in the recovery phase when opportunities for management or interruption of transmission have passed.[444]
• The duration of the persistence of antibodies produced in response to SARS-CoV-2 is still under investigation.[444] Some people may not develop detectable antibodies after infection, and in those who do, antibody levels may wane over time to undetectable levels.[518] The presence of antibodies that bind to SARS-CoV-2 does not guarantee that they are neutralizing antibodies, or that they offer protective immunity.[444]
• Some tests may exhibit cross-reactivity with other coronaviruses, such as those that cause the common cold, which can result in false-positive results.[518]
• Tests should not be used to determine the immune status of an individual, or to make decisions about grouping people residing in or being admitted to congregate settings (e.g., schools, dormitories, correctional facilities) or people returning to their workplace.[518]

Rapid diagnostic tests

Antibody detection

• While rapid antibody detection kits have been approved for the qualitative detection of SARS-CoV-2 IgG/IgM antibodies in serum, plasma, or whole blood, the WHO does not recommend the use of these tests outside of research settings as they have not been validated as yet.[523]

• Evidence is particularly weak for point-of-care serologic tests. A meta-analysis found that the overall sensitivity of chemiluminescent immunoassays (CLIA) for IgG or IgM was approximately 98%, and the sensitivity of enzyme-linked immunosorbent assays (ELISA) was 84%; however, lateral flow immunoassays (LFA), which have been developed as point-of-care tests, had the lowest sensitivity at 66%. Test sensitivity was highest 3 or more weeks after onset of symptoms. Available evidence does not support the use of existing point-of-care serologic tests.[524]

Antigen detection

• Antigen testing relies on direct detection of SARS-CoV-2 viral proteins in nasal swabs and other respiratory specimens using a lateral flow immunoassay. Results are usually available in less than 30 minutes. While antigen tests are substantially less sensitive than RT-PCR, they offer the possibility of rapid, inexpensive, and early detection of the most infectious cases in appropriate settings. If used, testing should occur within the first 5 to 7 days following the onset of symptoms.[525]

• The WHO recommends antigen testing only in certain scenarios where RT-PCR is unavailable or where prolonged turnaround times preclude clinical utility, provided that the test meets the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared with an RT-PCR reference assay.[525]

• The FDA has warned that false-positive results can occur with antigen tests, including when users do not follow the instructions for use, and that the number of false-positive tests increases as disease prevalence decreases.[526]

• Antigen testing has demonstrated a higher positive predictive value (90%) than RT-PCR (70%) compared with viral culture results. The positive percentage agreement for detection of infectious virus for the antigen test was similar to RT-PCR when compared with culture results.[527]

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

Chest imaging

All imaging procedures should be performed according to local infection prevention and control procedures to prevent transmission. Chest imaging is considered safe in pregnant women.[528]

Order a chest x-ray in all patients with suspected pneumonia. Unilateral lung infiltrates are found in 25% of patients, and bilateral lung infiltrates are found in 75% of patients.[49] [50] [529] 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.[530]

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.\[531\] 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.\[447\] [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.\[532\]
- 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.\[533\]

Chest CT has a sensitivity for diagnosis of COVID-19 in excess of 90% in symptomatic adults. However, the specificity is lower, with a range between 25% and 83%. Accuracy appears to be lower among children; however, there are limited data in this population.\[534\]

Abnormal chest CT findings have been reported in up to 97% of COVID-19 patients in one meta-analysis of 50,466 hospitalized patients.\[535\] Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.\[536\] 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).\[537\] Some patients may present with a normal chest finding despite a positive RT-PCR.\[538\] Also, 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.\[539\] Pregnant women appear to present more commonly with more advanced CT findings compared with the general adult population; however, results are similar to those in the general adult population.\[540\] CT is more sensitive than RT-PCR in detecting COVID-19, but has a very low specificity.\[541\]

Typical features

- 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.\[542\]
- Ground-glass opacity has the highest diagnostic performance for COVID-19 pneumonia, followed by ground-glass opacity plus consolidation, and consolidation only.\[543\] 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%).\[544\]
- 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.\[542\]
• 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.[545]
• Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity and, less frequently, nonspecific patchy shadows, areas of consolidation, and a halo sign. Abnormalities are more common in the lower lobes and are predominantly unilateral. Pleural effusion is rare. Children may have signs of pneumonia on chest imaging despite having minimal or no symptoms.[546]

Atypical features

• Pulmonary vascular enlargement, interlobular or intralobular septal thickening, adjacent pleural thickening, air bronchograms, subpleural lines, crazy-paving pattern, bronchus distortion, bronchiectasis, vacuolar retraction sign, and halo sign are atypical features. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have also been reported rarely.[542]

The WHO recommends chest imaging in the following scenarios:[530]

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

Emerging tests

Reverse transcription loop-mediated isothermal amplification

• Reverse transcription loop-mediated isothermal amplification (RT-LAMP) assays are an emerging test to detect SARS-CoV-2 viral RNA. While assays are simple and quick, there is less evidence for their use. Assays for SARS-CoV-2 have been developed and are being evaluated.[547] [548] [549]

Lung ultrasound

• Lung ultrasound is used as a diagnostic tool in some centers as an alternative to chest x-ray and chest CT. Although there is only very low-certainty evidence supporting its diagnostic accuracy, it might be helpful as a supplemental or alternate imaging modality.[530] It has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, easier sterilization process, absence of ionizing radiation exposure, and repeatability during follow-up. It may also be more readily available in resource-limited settings. However, it also has some limitations (e.g., it is unable to discern chronicity of a lesion) and other imaging modalities may be required. B-lines are the prominent pattern in patients with COVID-19, occurring with a pooled frequency of 97%. Pleural line abnormalities are also common, with a pooled frequency of 70%. While these findings are not specific for COVID-19, they increase the likelihood of disease in the context of a
characteristic clinical presentation. Other findings include consolidations, pleural thickening, and pleural effusion.[550] Ultrasound may be used in pregnant women and children.[551] [552]

- 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).[553]

Viral isolation

- Viral isolation is not recommended as a routine diagnostic procedure. All procedures involving viral isolation in cell culture require trained staff and biosafety level 3 (BSL-3) facilities.[444]

Calprotectin

- Calprotectin is an emerging biomarker of interest. Calprotectin levels often increase following infection or trauma, and in inflammatory disease. Serum/fecal calprotectin levels have been demonstrated to be significantly elevated in COVID-19 patients with severe disease, and it may have prognostic significance.[554]

History and exam

Key diagnostic factors

fever (common)

- Reported in approximately 77% of patients.[139] In one case series, only 44% of patients had a fever on presentation, but it developed in 89% of patients after hospitalization.[555] 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.[556]

cough (common)

- Reported in approximately 68% of patients.[139] The cough is usually dry; however, a productive cough has been reported in some patients.

dyspnea (common)

- Reported in approximately 38% of patients.[139] Median time from onset of symptoms to development of dyspnea is 5 to 8 days.[49] [50] [557] May last weeks after initial onset of symptoms. Wheeze has been reported in 17% of patients.[558]

altered sense of smell/taste (common)

- Presence of anosmia and/or ageusia may be useful as a red flag for diagnosis.[443] Olfactory dysfunction (anosmia/hyposmia) has been reported in approximately 41% of patients, and gustatory dysfunction (ageusia/dysgeusia) has been reported in approximately 35% of patients.[139] Prevalence appears to be higher in European studies.[559] May be an early symptom before the onset of other symptoms, or may be the only symptom in patients with mild to moderate illness.[560] Prevalence of anosmia/ageusia presenting before other symptoms was 13% to 73%, at the same time as other symptoms was 14% to 39%, and after other symptoms was 27% to 49%.[561] Complete resolution or improvement in symptoms was reported in 89% of patients 4 weeks after onset.[562] Anosmia
Coronavirus disease 2019 (COVID-19)

Diagnosis

or hyposmia is significantly associated with an enhanced risk of testing positive for COVID-19, and is a good predictor of infection. Many drugs are associated with taste and smell changes (e.g., antibiotics, ACE inhibitors) and should be considered in the differential diagnosis.

Other diagnostic factors

fatigue (common)

• Reported in approximately 30% of patients. Patients may also report malaise. Fatigue and exhaustion may be extreme and protracted, even in patients with mild disease.

myalgia or arthralgia (common)

• Reported in approximately 17% (myalgia) and 11% (arthralgia) of patients. Arthritis has been reported rarely.

sputum production/expectoration (common)

• Reported in approximately 18% of patients.

chest tightness (common)

• Reported in approximately 22.9% of patients.

gastrointestinal symptoms (common)

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

sore throat (common)

• Reported in approximately 16% of patients. Usually presents early in the clinical course.

headache (common)

• Reported in approximately 16% of patients.

dizziness (common)

• Reported in approximately 11% of patients.

neurologic symptoms (common)

• Confusion has been reported in approximately 11% of patients. Prevalence of confusion/delirium and agitation is high (65% and 69%, respectively) in patients in the intensive care unit. Delirium is associated with an increased risk of mortality in hospitalized older patients. Benzodiazepine use and the lack of family visitation (virtual or in-person) have been identified as risk factors for delirium. The pooled prevalence of anxiety, depression, and insomnia is 15.2%, 16%, and 23.9%,
respectively.[575] Altered mental status was as common in younger hospitalized patients (<60 years) as it was in older patients in one study.[576][577]

ocular symptoms (common)

- Reported in 11% of patients. The most common ocular symptoms include dry eye or foreign body sensation (16%), redness (13.3%), tearing (12.8%), itching (12.6%), eye pain (9.6%), and discharge (8.8%). Conjunctivitis was the most common ocular disease in patients with ocular manifestations (88.8%).[578] Most symptoms are mild and last for 4 to 14 days with no complications. Prodromal symptoms occur in 12.5% of patients.[579] Mild ocular symptoms (e.g., conjunctival discharge, eye rubbing, conjunctival congestion) were reported in 22.7% of children in one cross-sectional study. Children with systemic symptoms were more likely to develop ocular symptoms.[580]

rhinorrhea/nasal congestion (uncommon)

- Rhinorrhea has been reported in approximately 8% of patients, and nasal congestion has been reported in approximately 5% of patients.[558]

audio-vestibular symptoms (uncommon)

- Sudden sensorineural hearing loss, tinnitus, and rotatory vertigo have been reported in 7.6%, 14.8%, and 7.2% of patients, respectively. Otalgia has also been reported.[581]

chest pain (uncommon)

- Reported in approximately 7% of patients.[558] May indicate pneumonia.

cutaneous symptoms (uncommon)

- The pooled prevalence of overall cutaneous lesions is 5.7%. The most common symptoms are a viral exanthem-like presentation (4.2%), maculopapular rash (3.8%), and vesiculobullous lesions (1.7%). Other manifestations include urticaria, chilblain-like lesions, livedo reticularis, and finger/toe gangrene.[582] In the UK COVID Symptom Study, 17% of respondents reported rash as the first symptom of disease, and 21% of respondents reported rash as the only clinical sign.[583] It is unclear whether skin lesions are from viral infection, systemic consequences of the infection, or drugs the patient may be on. Further data is required to better understand cutaneous involvement.


lower urinary tract symptoms (uncommon)

- There is emerging evidence that patients may rarely have signs, symptoms, and radiologic and laboratory features indicative of involvement of the lower urinary tract and male genital system. This may include scrotal discomfort, swelling, or pain (acute orchitis, epididymitis, or epididymo-orchitis), low-flow priapism, impaired spermatogenesis, bladder hemorrhage, acute urinary retention, and worsening of existing lower urinary tract symptoms. Further research is required.[584]

hemoptysis (uncommon)

- Reported in approximately 2% of patients.[558] May be a symptom of pulmonary embolism.[585]

bronchial breath sounds (uncommon)

- May indicate pneumonia.

tachypnea (uncommon)

- May be present in patients with acute respiratory distress.
tachycardia (uncommon)
- May be present in patients with acute respiratory distress.

cyanosis (uncommon)
- May be present in patients with acute respiratory distress.

crackles/rales on auscultation (uncommon)
- May be present in patients with acute respiratory distress.

**Risk factors**

**Strong**

**contact with probable or confirmed case**
- People who have been in contact with a probable or confirmed case are at increased risk of infection.
- The World Health Organization defines a contact as a person who has experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case: face-to-face contact with a probable or confirmed case within 3 feet (1 meter) and for at least 15 minutes; direct physical contact with a probable or confirmed case; direct care for a patient with probable or confirmed COVID-19 without using recommended personal protective equipment; or other situations as indicated by local risk assessments.[190]
- The Centers for Disease Control and Prevention defines a close contact as someone who has been within 6 feet (2 meters) of an infected person for at least 15 minutes over a 24-hour period, beginning 2 days before symptom onset (or 2 days before testing in asymptomatic patients).[191]

**residence/work/travel in location with high risk of transmission**
- People who live or work in, or travel to, a location with a high risk of transmission are at increased risk of infection.
- People residing or working in an area with a high risk of transmission (e.g., closed residential settings, humanitarian setting), people residing in or traveling to an area with community transmission, and people working in a health setting (including within health facilities and households) at any time within the 14 days prior to symptom onset are at higher risk of infection.[190]
- People at risk of infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern include: those who have been in, or transited through, any countries with transmission of variants of concern (consult local guidance for lists of affected countries) and who develop symptoms within 10 days of departure or transit (or date of sampling for a positive SARS-CoV-2 test if asymptomatic); those known to be infected with a variant of concern based on sequencing results, regardless of travel history; contacts of these individuals.[192]

**older age**
- Older people are at increased risk for infection and severe disease.[193]
- In the UK, data from a cross-sectional study indicated that people aged 40 to 64 years are at greatest risk of infection, followed by patients 75 years and older, and then people aged 65 to 74 years.[194] The highest mortality rate was observed in patients 80 years and older.[195]
• 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.[7]
• 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.

**male sex**

• Males are at increased risk for infection and severe disease.[196]
• In the UK, data from a cross-sectional study found that the adjusted odds of a positive test were greater in males (18.4%) compared with females (13.3%).[194]
• It has been hypothesized that this may be due to the presence of androgens, a lower level of SARS-CoV-2 antibodies compared with females, women mounting a stronger immune response compared with men, genetic factors, or a higher prevalence of alcohol consumption and smoking; however, further research is required.[197] [198]

**ethnicity**

• People who belong to Black, Asian, and minority ethnic (BAME) groups are at increased risk of infection and severe disease.[199] [200]
• In the UK, data from a cross-sectional study found that South Asian and Black patients had 1.93 and 1.47 the odds of suspected infection, respectively.[201] The average age of patients from ethnic minorities was significantly lower than that of White patients.[202] Ethnic minorities in the UK (including South Asian, East Asian, Black, and other ethnic minorities) admitted to hospital were more likely to be admitted to intensive care and require invasive mechanical ventilation compared with White patients, despite similar disease severity at admission and being younger with fewer comorbidities.[203]
• In the US, age-adjusted data from the Centers for Disease Control and Prevention (as of 23 January 2021) indicate that Hispanic or Latino people, non-Hispanic American Indian or Alaska Native people, and non-Hispanic Black people have approximately 3.6, 3.2, and 2.9 times the rate of hospitalizations of non-Hispanic White people, respectively.[204] However, cohort studies in the US have found no difference in outcomes between non-Hispanic Black and Hispanic patients compared with White patients after adjusting for sociodemographic factors (e.g., age, sex, insurance) and comorbidities. These patients may have an increased risk of mortality and morbidity due to their disproportionate representation among hospitalizations.[205] [206] [207]
• Racial disparities in outcomes may be partially attributed to higher rates of comorbidities in certain ethnic groups.[208]

**residence in a long-term care facility**

• People in a long-term care facility are at increased risk for infection and severe disease.[122] [209]
• 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.[210] 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.[211]
• 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.[212]
presence of comorbidities

- People with comorbidities are at increased risk for severe disease, and the more comorbidities, the greater the risk.[213] [214]
- 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%).[6]
- In the US, approximately 91% of hospitalized adults had at least one reported underlying medical condition, with the most common being hypertension (56%), obesity (49%), metabolic disease (42%), and cardiovascular disease (33%). Approximately 53% of children had at least one reported underlying medical condition, with the most common being obesity (37%), neurologic disease (13%), and asthma (12%).[204] 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.[215] [216]
- 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.[217]

obesity

- People with obesity are at increased risk for infection and severe disease.[218]
- 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.[219]
- People with obesity (≥30 kg/m²) or severe obesity (≥40 kg/m²) are at increased risk for severe disease. People who are overweight (25-30 kg/m²) may be at increased risk of severe disease; however, evidence is limited.[214] Evidence from a meta-analysis suggests a linear dose-response association between body mass index and disease severity and mortality.[220] However, a cohort study in the US found a nonlinear relationship between body mass index and disease severity, with the lowest risk at body mass indexes near the threshold between healthy weight and overweight, then increasing with higher body mass index.[221]
- Obesity is associated with an increased risk for disease progression, hospitalization, intensive care unit admission, need for invasive mechanical ventilation, complications (e.g., venous thromboembolism and renal failure), and in-hospital mortality, especially among younger patients.[218] [222] [223]

cardiocascular disease

- People with cardiovascular disease are at increased risk for severe disease.[214]
- 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.[224]
- People with risk factors for cardiovascular disease (e.g., hypertension, diabetes) are also at increased risk for severe disease and mortality (see below).[225] [226]

diabetes

- People with type 2 diabetes are at increased risk for severe disease. People with type 1 diabetes or gestational diabetes may be at increased risk for severe disease; however, evidence is limited.[214]
Diabetes is associated with an increased risk for disease progression, intensive care admission, acute respiratory distress syndrome, need for invasive mechanical ventilation, and mortality.\[227\] \[228\] In the UK, one third of all deaths in hospitalized patients occurred in patients with diabetes.\[229\] An analysis of more than 19,000 patients admitted to critical care over the entire first wave of the pandemic found that type 2 diabetes is associated with a 20% increase in mortality in patients with severe disease, independent of age, sex, ethnicity, obesity, or other major comorbidity.\[230\] Risk factors for poor prognosis and higher mortality in patients with type 1 or type 2 diabetes include older age, male sex, non-White ethnicity, socioeconomic deprivation, renal impairment, history of stroke or heart failure, higher glycosylated hemoglobin (HbA1c) levels, higher body mass index, elevated C-reactive protein, diabetic ketoacidosis, and insulin use.\[231\] \[232\] \[233\] However, HbA1c levels were not associated with mortality in a large US cohort of hospitalized patients.\[234\] Patients with newly diagnosed diabetes have a higher risk of all-cause mortality compared with patients with known diabetes, hyperglycemia, or normal glucose.\[235\] Metformin use has been associated with lower mortality.\[236\]

The poor prognosis in these patients is likely due to the syndromic nature of diabetes, with factors such as hyperglycemia, older age, and the presence of comorbidities (e.g., obesity, hypertension, cardiovascular disease) all contributing to the increased risk.\[237\]

### Chronic respiratory disease

- People with chronic obstructive pulmonary disease COPD, including emphysema and chronic bronchitis, are at increased risk for severe disease. People with moderate to severe asthma, or other chronic lung diseases (e.g., cystic fibrosis, idiopathic pulmonary fibrosis) may be at increased risk for severe disease; however, evidence is limited.\[214\]
- COPD is associated with a more than 3-fold increased risk for severe disease and mortality.\[238\] A national, multicenter prospective cohort study in the UK (75,463 patients from 258 healthcare facilities) found that patients with COPD were less likely to receive critical care than patients without an underlying respiratory condition.\[239\]
- Data are insufficient to conclude whether asthma is a risk factor for infection, hospitalization, intensive care unit admission, or death.\[240\] According to meta-analyses, asthma is not associated with an increased risk for infection, severe disease, worse prognosis, or a higher risk of intubation or mechanical ventilation. Clinical outcomes were similar between patients with asthma and patients without asthma. Patients with asthma had a lower risk of death compared with nonasthmatic patients.\[241\] \[242\] However, a national, multicenter prospective cohort study in the UK (75,463 patients from 258 healthcare facilities) found that patients with asthma were more likely to receive critical care than patients without an underlying respiratory condition. Severe asthma was associated with increased mortality compared with patients with nonsevere asthma in patients ages 16 years and older. Inhaled corticosteroid use in patients with asthma was associated with lower mortality compared with patients without an underlying respiratory condition in patients ages 50 years and older.\[243\]
- People with obstructive sleep apnea may be at increased risk for severe disease independent of age, sex, body mass index, and comorbidities; however, evidence is limited. Obstructive sleep apnea has not been associated with an increased risk of infection.\[244\]
- There are no data on whether pediatric respiratory diseases (including childhood asthma) are risk factors for infection or severity.\[245\] There is no clear evidence that people with asthma or COPD are at higher risk of infection.\[246\] \[247\]
chronic kidney disease

- People with chronic kidney disease are at increased risk for severe disease, and may be at higher risk for infection.[194] [214]
- 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%).[194]
- Preexisting chronic kidney disease is an independent risk factor for developing acute kidney injury as a complication.[248]

pregnancy

- Pregnant women are at increased risk for severe disease.[214]
- 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.[27]
- See the Complications section for more information on pregnancy-related complications.

smoking

- People who are current or former smokers are at increased risk for severe disease.[214]
- 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. Current smokers are at higher risk of developing severe disease compared with nonsmokers.[249] Smokers have double the mortality risk compared with nonsmokers.[250] This may be due to increased airway expression of the angiotensin-converting enzyme-2 receptor in smokers.[251]
- The World Health Organization has reviewed the available evidence and concluded that smoking is associated with increased severity of disease and death in hospitalized patients.[252]

malignancy

- People with cancer are at increased risk for infection and severe disease.[214] [253]
- A higher risk of infection is likely due to immunosuppressive treatments and/or recurrent hospital visits.[253]
- Patients with cancer are 76% more likely to get severe disease compared with those without cancer.[254] They also have an increased risk for deterioration, intensive care unit admission, and all-cause mortality (particularly those with metastatic disease, hematologic cancer, or lung cancer).[255] [256] The odds ratio of intensive care admission rates and mortality rates between cancer and noncancer groups was 2.88 and 2.25, respectively.[257] The pooled in-hospital mortality risk in patients with cancer is 14.1%.[258]
- Risk factors for mortality include male sex, older age, presence of one or more comorbidities, hypertension, COPD, and the presence of complications (e.g., acute respiratory distress syndrome, acute renal failure). Patients with hematologic malignancies have an increased risk of mortality compared with those with solid tumors.[259] While active chemotherapy or chemotherapy within the last 30 days increased the risk of death, targeted therapies, immunotherapy, surgery, and radiation therapy did not appear to increase the risk for severe disease or death.[260] [261]
- 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.[262] 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.[263]

**solid organ transplant**

- People with an immunocompromised state from solid organ transplant are at increased risk for severe disease.[214]
- 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. Overall mortality in solid organ transplant recipients was 20%.[264]
- Hospitalization and mortality rates in liver transplant recipients are disproportionately high compared with nontransplant patients regardless of age or time after transplant. Older age and diabetes are significant risk factors for death among these patients.[265]

**Down syndrome**

- People with Down syndrome are at increased risk for severe disease.[214]
- In the UK, a cohort study found a 4-fold increased risk for hospitalization and a 10-fold increased risk for mortality in people with Down syndrome.[266] This may possibly be due to the presence of immune dysfunction, congenital heart disease, and pulmonary pathology.

**hemoglobin disorders**

- People with sickle cell disease are at increased risk for severe disease. People with thalassemia may be at increased risk for severe disease; however, evidence is limited.[214]
- 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.[267] Infection can cause acute chest syndrome in patients with sickle cell disease.[268] [269]

**hypertension**

- People with hypertension may be at increased risk for severe disease; however, evidence is limited.[214]
- 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.[270] 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.[271] [272]
- 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.[273] 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.[274] [275]

**cerebrovascular disease**

- People with cerebrovascular disease may be at increased risk for severe disease; however, evidence is limited.[214]
- Patients with a history of cerebrovascular disease were more likely to progress to adverse outcomes compared with patients without a history of cerebrovascular disease.[276] Patients with preexisting
cerebrovascular disease had 2.67-fold higher odds of poor outcomes including intensive care admission, mechanical ventilation, and mortality.\[277\]

**dementia**

- People with dementia may be at increased risk for infection and severe disease; however, evidence is limited.\[214\] [278]
- 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.\[279\]
- 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.\[280\]

**chronic liver disease**

- People with chronic liver disease, especially cirrhosis, may be at increased risk for severe disease; however, evidence is limited.\[214\]
- Chronic liver disease has been associated with an increased risk for severe disease and mortality.\[281\] The 30-day mortality rate is higher in patients with cirrhosis, with the main causes of death being respiratory complications and sudden worsening of liver function leading to end-stage liver disease.\[282\]
- People with metabolic dysfunction-associated fatty liver disease (nonalcoholic fatty liver disease) are at increased risk for severe disease. Disease severity has been associated with age <60 years and intermediate or high fibrosis-4 (FIB-4) scores.\[283\] [284\] [285\]

**immunosuppression**

- People who are immunocompromised may be at increased risk for severe disease; however, evidence is limited.\[214\]
- This includes people with a history of blood or bone marrow transplant, immune deficiencies, or prolonged use of corticosteroids or other immunosuppressant medications.
- Glucocorticoid exposure of ≥10 mg/day (prednisone) has been associated with a higher odds of hospitalization in patients with rheumatologic disease.\[286\] 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.\[287\]
- Immunosuppressed patients are not at significantly increased risk of infection compared with the general population.\[288\]
- Also see HIV infection and Autoimmune disease below.

**children with certain underlying conditions**

- Children with certain underlying conditions may be at increased risk for severe disease; however, evidence is limited.\[214\]
- These conditions include obesity, diabetes, asthma and chronic lung disease, immunosuppression, sickle cell disease, and chronic kidney disease. Children may also be at risk if they are medically complex; have serious genetic, neurologic, or metabolic disorders; or have congenital heart disease.\[214\]
Weak vitamin D deficiency

- People with vitamin D deficiency may be at higher risk for infection and severe disease; however, evidence is limited.[289] [290]
- Multiple observational and retrospective studies have found an association between vitamin D deficiency and a higher risk for infection. A meta-analysis of available data concluded that low serum vitamin D level was significantly associated with a higher risk of infection, and people with vitamin D deficiency were 80% more likely to be infected.[291]
- A meta-analysis found that vitamin D deficiency increased the risk for hospitalization and mortality, and patients with severe disease were more likely to have vitamin D deficiency compared with patients with mild disease.[292]
- A cross-sectional study in 235 hospitalized patients in Iran found that patients who had sufficient serum vitamin D levels at admission, defined as serum 25(OH)D level ≥30 nanograms/mL, had significantly lower blood levels of C-reactive protein and a higher total blood lymphocyte count compared with those with insufficient vitamin D levels, suggesting that sufficient vitamin D levels improved immune function in these patients. Severe disease was less prevalent in patients with adequate vitamin D levels, and among those ages 40 years and over who died approximately 90% had insufficient vitamin D levels.[293]

proton-pump inhibitor use

- People taking proton-pump inhibitors (PPIs) may be at increased risk for infection and severe disease; however, evidence is limited.
- PPIs are known to increase the risk of infections due to hypochlorhydria. There is evidence of an independent, dose-response relationship between the use of antisecretory medications and COVID-19 positivity. People taking PPIs had significantly increased odds for reporting a positive COVID-19 test when compared with those not taking PPIs. People taking H2 antagonists were not at elevated risk.[294]
- Patients taking PPIs may also be at increased risk for secondary infections, severe clinical outcomes, and death.[295] [296] 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.[297]

autoimmune disease

- People with autoimmune disease may be at higher risk for infection and severe disease; however, evidence is limited.[298]
- Autoimmune disease has been associated with an increased risk of infection. However, clinical outcomes were not considerably worse when compared with people without autoimmune disease. Use of corticosteroids increased the risk of infection and severe outcomes, and use of combination disease-modifying antirheumatic drugs (DMARDs) increased the risk of severe outcomes. DMARD monotherapy, particularly tumor necrosis factor inhibitors, reduced the risk of severe disease and mortality. Other factors associated with severe disease in this population include older age and the presence of comorbidities.[298]
- In patients with multiple sclerosis, neurologic disability, older age, Black race, cardiovascular comorbidities, recent treatment with corticosteroids, and obesity were risk factors for severe disease and mortality.[299] [300]
• In patients with inflammatory bowel disease, infection risk was comparable to the general population, and patient outcomes (hospitalization, intensive care unit admission, and mortality) were worse in ulcerative colitis and patients on corticosteroids, thiopurines, aminosalicylates, or combination therapy. Outcomes were better in patients on biologic agents.[301] [302] [303]

**HIV infection**

• People living with HIV may be at increased risk for mortality; however, evidence is limited and conflicting.

• It is still unclear whether HIV infection influences infection and disease course. A retrospective cohort study in the UK found that people with HIV appear to be at increased risk for mortality.[304] A retrospective cohort study in New York found that while people with HIV do not appear to be at increased risk of infection, they are at increased risk for poor outcomes (mainly higher rates of severe disease requiring hospitalization) compared with people living without diagnosed HIV infection. Hospitalization risk increased with progression of HIV disease stage.[305]

• Data from meta-analyses are conflicting. One meta-analysis found that HIV infection was not associated with composite poor outcome.[306] However, other meta-analyses have found that people living with HIV infection have an increased risk for infection and mortality compared with people without HIV. People on tenofovir disoproxil-based regimens may have a lower risk of infection and poor outcomes; however, evidence is inconclusive.[307] [308]

**dyslipidemia**

• Dyslipidemia appears to be associated with an increased risk for severe disease and mortality; however, evidence is limited.[309] [310]

• The association was stronger in males, older age, and those with hypertension.[311]

• 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.[273] However, so far, studies do not support this hypothesis, and some studies have shown a protective effect.[312] [313] [314] [315]

**surgery**

• Surgical mortality and complications may be higher in patients with COVID-19 compared with patients without COVID-19.[316]

• 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.[317]

• 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.[318]

**blood groups A and B**

• People with blood group A may be at increased risk for infection and mortality, and people with blood group B may be at increased risk for infection; however, evidence is limited.[319]

• There is no evidence for an association between blood group AB and the risk of infection. Blood group O appears to be protective against infection. People who are Rh-positive were more vulnerable to infection compared with those who were Rh-negative.[320]
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.[189] 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.[321]

gut dysbiosis

- There is limited evidence that gut microbiota dysfunction may be implicated in the pathogenesis of COVID-19.
- 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.[322] [323] [324] 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.[325]

environmental factors

- Climate and latitude: limited evidence suggests that cold and dry conditions and higher latitude may increase transmission, and warm and humid conditions may reduce the rate of infections; however, evidence is conflicting and is not sufficient to prove causation.[326] [327] [328] [329] [330] [331] [332]
- Air pollution: limited evidence suggests an association between exposure to ambient air pollution and COVID-19; however, evidence is not sufficient to prove causation.[333] [334] [335] [336]
- Residence in urban or deprived areas: limited evidence suggests that the adjusted odds of a positive test were greater in people living in urban areas (26.2%) compared with people living in rural areas (5.6%), and in people living in more deprived areas (29.5%) compared with people living in less deprived areas (7.7%).[194]
# Investigations

## 1st test to order

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

- **Important:** the US Food and Drug Administration has warned that false-negative results may occur with any molecular test for the detection of SARS-CoV-2 if a mutation occurs in the part of the virus’ genome assessed by that test. Multiple genetic targets to determine a final result are less likely to be impacted by increased prevalence of genetic variants. Consider negative results in combination with clinical observations, patient history, and epidemiologic information.[586]

- Order an RT-PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with suspected infection whenever possible (see the Criteria section).[444] Commonly used assays are expected to be able to detect SARS-CoV-2 variants of concern.[192]

- Molecular testing is an aid to diagnosis only. The World Health Organization recommends that healthcare providers consider a positive or negative result in combination with specimen type, clinical observations, patient history, and epidemiologic information. Where a test result does not correspond with the clinical presentation, a new specimen should be taken and retested using the same or a different molecular test.[489]

- Base decisions about who to test on clinical and epidemiologic factors.[444] Consult local health authorities for guidance as testing priorities depend on local recommendations and available resources.

- In the UK, testing is recommended in: (1) people with symptoms of new continuous cough, high temperature, or altered sense of smell/taste; (2) people with acute respiratory infection, influenza-like illness, clinical or radiologic evidence of pneumonia, or acute worsening of underlying respiratory illness, or fever without another cause (whether presenting in primary or secondary care).[490]

- In the US, testing is recommended in: (1) people with symptoms, even if they are mild; (2) people who are asymptomatic and have been in close contact (less than 6 feet [2 meters] for a total of 15 minutes or more over a 24-hour period) with a person with documented infection; (3) people who are asymptomatic and have not been in close contact for at least 15 minutes with a person with documented infection only if required by a healthcare provider or public health official.[491]

- The American Academy of Pediatrics recommends testing children with symptoms consistent with COVID-19, children in close contact with an individual with probable or confirmed infection, and children who require screening based on recommendations from public health authorities or other situations (e.g., prior to a medical procedure such as elective surgery or as a school or workplace requirement). The decision to test does not differ by the age of the child. Testing is not recommended for other illnesses that lack shared symptoms (e.g., urinary tract infection, cellulitis), or for children exposed to close contacts of infected individuals unless those contacts are symptomatic or other criteria are met.[492]

- The optimal specimen for testing depends on the clinical presentation and the time since symptom onset. The World Health Organization...
## Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
</table>
| 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. 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.

- 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).

- The pooled sensitivity has been estimated to be 87.8%, with the specificity estimated to be in the range of 87.7% to 100%.

- Interpret test results with caution. Evidence for the use of RT-PCR in the diagnosis of COVID-19 is still emerging, and uncertainties about its efficacy and accuracy remain. It is not fully understood whether a positive result always represents infectious virus, especially at high cycle thresholds. Interpreting the result depends on the accuracy of the test itself, and the pre- and post-test probabilities of disease. When the pretest probability is low, positive results should be interpreted with caution, and ideally a second specimen tested for confirmation. The lower the prevalence of disease in a given population, the lower the post-test probability. False-positive results can be caused by a laboratory error or a cross-reaction with antibodies formed by current and past exposure to seasonal human coronavirus infections (e.g., common cold), and are more likely when the prevalence of disease is moderate to low. Preliminary estimates of the false-positive rate in the UK are in the range of 0.8% to 4%. False-negative rates of between 2% and 29% have been reported. 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.

- Also collect nasopharyngeal swabs to rule out influenza and other respiratory infections according to local guidance. It is important to note that coinfections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19. When SARS-CoV-2 and influenza viruses are cocirculating, test for both viruses in all hospitalized patients with acute respiratory illness, and only test for influenza virus in outpatients with acute respiratory illness if the results will change clinical management of the patient. Single-test multiplex assays to diagnose infection caused by influenza A, influenza B, and SARS-CoV-2 are available in some countries.

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## Test | Result
---|---
**pulse oximetry** | may show low oxygen saturation (cut-off depends on local guidelines)
- 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.[477]
- Pulse oximetry may be available as part of remote monitoring in the community. Evidence suggests that patients who may benefit most from monitoring are those who are symptomatic and are either over 65 years of age, or are under 65 years years of age and are extremely clinically vulnerable to COVID-19. [NHS England: pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings] (https://www.england.nhs.uk/coronavirus/publication/pulse-oximetry-to-detect-early-deterioration-of-patients-with-covid-19-in-primary-and-community-care-settings/)
- The UK National Institute for Health and Care Excellence recommends using oxygen saturation levels below 94% for adults (or below 88% for adults with known type 2 respiratory failure) and below 91% for children in room air at rest to identify people who are seriously ill.[478]
- Pulse oximeters may exhibit suboptimal accuracy in certain populations. Limited data from studies with small numbers of participants suggest that skin pigmentation can affect pulse oximeter accuracy. In one study, occult hypoxemia (defined in the study as arterial oxygen saturation <88% by arterial blood gas despite oxygen saturation of 92% to 96% on pulse oximetry) was not detected by pulse oximetry nearly three times more frequently in Black patients compared with White patients.[479] The US Food and Drug Administration (FDA) has warned that multiple factors can affect the accuracy of a pulse oximeter reading (e.g., poor circulation, skin pigmentation, skin thickness, skin temperature, current tobacco use, use of fingernail polish). The FDA recommends considering accuracy limitations when using a pulse oximeter to assist in diagnosis and treatment decisions, and to use trends in readings over time rather than absolute cut-offs if possible.[480]
- Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognizing further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[477]

**ABG** | may show low partial oxygen pressure
- 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 (SpO₂ <90%).

**CBC** | lymphopenia; leukocytosis; leukopenia; thrombocytopenia; decreased eosinophils; decreased hemoglobin
- 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.[590]
### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated red blood cell distribution width (at admission and increasing during hospitalization) has been associated with a significantly increased risk of mortality in hospitalized patients.</td>
<td>elevated liver enzymes; elevated total bilirubin; renal impairment; hypoalbuminemia; electrolyte derangements</td>
</tr>
<tr>
<td>Absolute counts of major lymphocyte subsets, particularly CD4+ and CD8+ T-cell counts, are significantly decreased in patients with severe disease.</td>
<td></td>
</tr>
<tr>
<td>Late-phase thrombocytopenia (i.e., occurring 3 weeks or more after symptom onset) has been reported but is uncommon.</td>
<td></td>
</tr>
<tr>
<td><strong>comprehensive metabolic panel</strong></td>
<td></td>
</tr>
<tr>
<td>Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>Elevated liver enzymes, total bilirubin, creatinine, and blood urea nitrogen, and hypoalbuminemia are significantly associated with severe disease, and may be useful for predicting disease progression.</td>
<td>elevated liver enzymes; elevated total bilirubin; renal impairment; hypoalbuminemia; electrolyte derangements</td>
</tr>
<tr>
<td>Hypokalemia has been reported in 54% of patients. Hypocalcemia has been reported in 63% of patients, and is associated with poor outcomes.</td>
<td></td>
</tr>
<tr>
<td><strong>blood glucose level</strong></td>
<td>variable</td>
</tr>
<tr>
<td>Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>High fasting blood glucose level on admission independently predicts poor prognosis.</td>
<td>elevated D-dimer; prolonged prothrombin time; elevated fibrinogen</td>
</tr>
<tr>
<td>Hypoglycemia has also been associated with increased mortality in a retrospective cohort study.</td>
<td></td>
</tr>
<tr>
<td><strong>coagulation screen</strong></td>
<td></td>
</tr>
<tr>
<td>Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>Elevated D-dimer, elevated fibrinogen (and fibrin degradation product), and prolonged prothrombin time are significantly associated with severe disease, and may be useful for predicting disease progression.</td>
<td>elevated D-dimer; prolonged prothrombin time; elevated fibrinogen</td>
</tr>
<tr>
<td>The risk of severe disease and mortality is 2-fold and 4-fold higher, respectively, in patients with elevated D-dimer levels.</td>
<td>elevated D-dimer; prolonged prothrombin time; elevated fibrinogen</td>
</tr>
<tr>
<td>Patients with very high D-dimer levels have an increased risk of thrombosis.</td>
<td>elevated D-dimer; prolonged prothrombin time; elevated fibrinogen</td>
</tr>
<tr>
<td><strong>cardiac biomarkers</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>may be elevated</td>
</tr>
<tr>
<td>CK-MB has been found to be elevated in mild disease in children. The significance of this is unknown.</td>
<td>may be elevated</td>
</tr>
<tr>
<td><strong>serum C-reactive protein</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>Elevated C-reactive protein is significantly associated with severe disease, and may be useful for predicting disease progression.</td>
<td>may be elevated</td>
</tr>
<tr>
<td>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.</td>
<td>may be elevated</td>
</tr>
<tr>
<td><strong>serum erythrocyte sedimentation rate</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Commonly elevated in patients with COVID-19.[484]</td>
<td>may be elevated</td>
</tr>
<tr>
<td><strong>serum lactate dehydrogenase</strong></td>
<td></td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated serum lactate dehydrogenase is significantly associated with severe disease, and may be useful for predicting disease progression.[590]</td>
<td>may be elevated</td>
</tr>
<tr>
<td><strong>serum interleukin-6 level</strong></td>
<td></td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated interleukin-6 level is significantly associated with severe disease, and may be useful for predicting disease progression.[590]</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Less likely to be elevated in children.[605]</td>
<td></td>
</tr>
<tr>
<td><strong>serum procalcitonin</strong></td>
<td></td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated serum procalcitonin is significantly associated with severe disease, and may be useful for predicting disease progression.[590]</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Elevated serum procalcitonin may be more common in children.[474] [50]</td>
<td></td>
</tr>
<tr>
<td>• May be elevated in patients with secondary bacterial infection.[49] [50]</td>
<td></td>
</tr>
<tr>
<td>• 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.[478]</td>
<td></td>
</tr>
<tr>
<td><strong>serum ferritin level</strong></td>
<td></td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated ferritin is significantly associated with severe disease, and may be useful for predicting disease progression.[606]</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• May indicate development of cytokine release syndrome.[607]</td>
<td></td>
</tr>
<tr>
<td><strong>serum amyloid A level</strong></td>
<td></td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[608]</td>
<td>may be elevated</td>
</tr>
<tr>
<td><strong>serum creatine kinase and myoglobin</strong></td>
<td></td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated serum creatine kinase and myoglobin are significantly associated with severe disease, and may be useful for predicting disease progression.[590]</td>
<td>may be elevated</td>
</tr>
<tr>
<td><strong>blood and sputum cultures</strong></td>
<td>negative for bacterial infection</td>
</tr>
<tr>
<td>• Collect blood and sputum specimens for culture in patients with severe or critical disease to rule out other causes of lower respiratory tract infection and sepsis, especially patients with an atypical epidemiologic history.[136]</td>
<td></td>
</tr>
<tr>
<td>• Specimens should be collected prior to starting empiric antimicrobials if possible.</td>
<td></td>
</tr>
<tr>
<td><strong>chest x-ray</strong></td>
<td>unilateral or bilateral lung infiltrates</td>
</tr>
<tr>
<td>• Order in all patients with suspected pneumonia.</td>
<td></td>
</tr>
<tr>
<td>• Unilateral lung infiltrates are found in 25% of patients, and bilateral lung infiltrates are found in 75% of patients.[49] [50] [529]</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>------</td>
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</tr>
<tr>
<td>• 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.</td>
<td>[530]</td>
</tr>
</tbody>
</table>
## Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>computed tomography (CT) chest</td>
<td>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</td>
</tr>
<tr>
<td>• 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. <a href="https://www.bsti.org.uk/media/resources/files/NHSE_BSTI_APPROVED_Radiology_on_CoVid19_v6_modified1__Read-Only.pdf">BSTI: radiology decision tool for suspected COVID-19</a> 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. [532] 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. [533] • Chest CT has a sensitivity for diagnosis of COVID-19 in excess of 90% in symptomatic adults. However, the specificity is lower, with a range between 25% and 83%. Accuracy appears to be lower among children; however, there are limited data in this population. [534] • Abnormal chest CT findings have been reported in up to 97% of hospitalized patients. [535] Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients. [536] 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). [609] Some patients may present with a normal chest finding despite a positive RT-PCR. [538] Also, 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. [539] • The most common findings are ground-glass opacity, either in isolation or coexisting with other findings such as consolidation, interlobular septal thickening, or crazy-paving pattern. The most common distribution pattern is bilateral, peripheral/subpleural, posterior distribution of the opacities, with a lower lobe predominance. Extensive/multilobar involvement with consolidations is more common in older patients and those with severe disease. Pulmonary vascular enlargement, interlobular or intralobular septal thickening, adjacent pleural thickening, air bronchograms, subpleural lines, crazy-paving pattern, bronchus distortion, bronchiectasis, vascular retraction sign, and halo sign are atypical features. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have also been reported rarely. [542] Ground-glass opacity has the highest diagnostic performance for COVID-19 pneumonia, followed by ground-glass opacity plus consolidation, and consolidation only. [543] • Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity and, less frequently, nonspecific patchy shadows, areas of consolidation, and a halo sign. Abnormalities are more common in the lower lobes and are predominantly unilateral. Pleural effusion is rare. [546] • CT scan generally shows an increase in the size, number, and density of ground-glass opacities in the early follow-up period, with a...</td>
<td></td>
</tr>
</tbody>
</table>
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. [542]

- 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. [610] [611] 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%). [544]

- CT is more sensitive than RT-PCR in detecting COVID-19, but has a very low specificity. [612] In a cohort of over 1000 patients in a hyperendemic area in China, chest CT had a higher sensitivity for diagnosis of COVID-19 compared with initial RT-PCR from swab samples (88% versus 59%). Improvement of abnormal CT findings also preceded change from RT-PCR positivity to negativity in this cohort during recovery. The sensitivity of chest CT was 97% in patients who ultimately had positive RT-PCR results. However, in this setting, 75% of patients with negative RT-PCR results also had positive chest CT findings. Of these patients, 48% were considered highly likely cases, while 33% were considered probable cases. [613]

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>CT is more sensitive than RT-PCR in detecting COVID-19, but has a very low specificity.</td>
<td></td>
</tr>
</tbody>
</table>

**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

**serology**

- Important: a positive test for spike protein IgM or IgG could indicate either prior infection or prior vaccination with a COVID-19 vaccine. To evaluate for evidence of prior infection in an individual who positive for SARS-CoV-2 virus antibodies; seroconversion or a rise in
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>has received a vaccine, a test that specifically evaluates IgM or IgG to the nucleocapsid protein should be used. A positive nucleocapsid protein-based assay indicates prior infection. Antibody testing is not currently recommended to assess immunity following vaccination.</td>
<td>antibody titers in paired sera</td>
</tr>
<tr>
<td>• Cannot be used as a standalone diagnostic for acute infections; however, may be useful in various settings (e.g., negative molecular testing, diagnosing patients with late presentation or prolonged symptoms, serosurveillance studies).</td>
<td></td>
</tr>
<tr>
<td>• <a href="https://www.bmj.com/content/370/bmj.m3325">BMJ practice pointer: testing for SARS-CoV-2 antibodies</a></td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>• The Centers for Disease Control and Prevention recommends serologic testing as a method to support the diagnosis of acute infection in patients who present late (i.e., 9 to 14 days after symptom onset) in addition to other viral detection methods (e.g., RT-PCR, antigen detection tests), or patients who present with late complications (e.g., pediatric inflammatory multisystem syndrome in children).</td>
<td></td>
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<tr>
<td>• The Infectious Diseases Society of America recommends serologic testing in the following circumstances: evaluation of patients with a high clinical suspicion for infection when molecular diagnostic testing is negative and at least 2 weeks have passed since symptom onset; evaluation of pediatric inflammatory multisystem syndrome in children; and serosurveillance studies.</td>
<td></td>
</tr>
<tr>
<td>• Antibody responses to SARS-CoV-2 typically occur during the first 1 to 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.</td>
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<tr>
<td>• The estimated sensitivity of antibody tests ranged from 18.4% to 96.1% (the lowest reported sensitivity was from a point-of-care test, although a sensitivity &lt;50% was reported for one laboratory test), and specificity ranged from 88.9% to 100%. Estimates of diagnostic accuracy need to be interpreted with caution in the absence of a definitive reference standard to diagnose or rule out COVID-19.</td>
<td></td>
</tr>
<tr>
<td>• Limitations of testing: serologic testing cannot be used to determine acute infection; results do not indicate the presence or absence of current or previous infection with certainty; reliable diagnosis is often only possible in the recovery phase when opportunities for management or interruption of transmission have passed; cross-reactivity with other coronaviruses, which can result in false-positive results.</td>
<td></td>
</tr>
<tr>
<td>• While rapid antibody detection kits have been approved for the qualitative detection of SARS-CoV-2 IgG/IgM antibodies in serum, plasma, or whole blood, the WHO does not recommend the use of these tests outside of research settings as they have not been validated as yet.</td>
<td></td>
</tr>
</tbody>
</table>
### Diagnosis

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

- Rapid diagnostic test. Relies on direct detection of SARS-CoV-2 viral proteins in nasal swabs and other respiratory specimens using a lateral flow immunoassay. Results are usually available in less than 30 minutes. While antigen tests are substantially less sensitive than RT-PCR, they offer the possibility of rapid, inexpensive, and early detection of the most infectious cases in appropriate settings. If used, testing should occur within the first 5 to 7 days following the onset of symptoms. The World Health Organization recommends antigen testing only in certain scenarios where RT-PCR is unavailable or where prolonged turnaround times preclude clinical utility, provided that the test meets the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared with an RT-PCR reference assay.[525]
- The US Food and Drug Administration has warned that false-positive results can occur with antigen tests, including when users do not follow the instructions for use, and that the number of false-positive tests increases as disease prevalence decreases.[526]
- Rapid, lateral flow antigen tests for home use are available over-the-counter in some countries.[614]
- Laboratory-based (nonrapid) antigen tests are also available in some countries.
## Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>reverse transcription loop-mediated isothermal amplification</strong></td>
<td><strong>positive for SARS-CoV-2 viral RNA</strong></td>
</tr>
<tr>
<td>(RT-LAMP)</td>
<td></td>
</tr>
<tr>
<td>• A similar process to RT-PCR, but uses constant temperatures and</td>
<td></td>
</tr>
<tr>
<td>produces more viral DNA compared with RT-PCR. While simple and</td>
<td></td>
</tr>
<tr>
<td>quick, it is a newer technology and there is less evidence for its</td>
<td></td>
</tr>
<tr>
<td>use. Assays for SARS-CoV-2 have been developed and are being</td>
<td></td>
</tr>
<tr>
<td>evaluated.[547] [548] [549]</td>
<td></td>
</tr>
<tr>
<td>• An at-home test kit that provides rapid results within 30 minutes</td>
<td></td>
</tr>
<tr>
<td>has been approved in the US under an emergency-use authorization for</td>
<td></td>
</tr>
<tr>
<td>self-testing at home that provides rapid results.[615]</td>
<td></td>
</tr>
<tr>
<td><strong>lung ultrasound</strong></td>
<td><strong>B-lines; pleural line abnormalities</strong></td>
</tr>
<tr>
<td>• Lung ultrasound is used as a diagnostic tool in some centers as</td>
<td></td>
</tr>
<tr>
<td>an alternative to chest x-ray and chest CT. Although there is only</td>
<td></td>
</tr>
<tr>
<td>very low-certainty evidence supporting its diagnostic accuracy, it</td>
<td></td>
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<tr>
<td>might be helpful as a supplemental or alternate imaging modality.</td>
<td></td>
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<tr>
<td>[530]</td>
<td></td>
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<tr>
<td>• Has the advantages of portability, bedside evaluation, reduced</td>
<td></td>
</tr>
<tr>
<td>healthcare worker exposure, easier sterilization process, absence</td>
<td></td>
</tr>
<tr>
<td>of ionizing radiation exposure, and repeatability during follow-up.</td>
<td></td>
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<tr>
<td>It may also be more readily available in resource-limited settings.</td>
<td></td>
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<tr>
<td>However, it also has some limitations (e.g., it is unable to</td>
<td></td>
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<tr>
<td>discern chronicity of a lesion) and other imaging modalities may</td>
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<tr>
<td>be required.</td>
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<tr>
<td>• B-lines are the prominent pattern in patients with COVID-19,</td>
<td></td>
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<tr>
<td>occurring with a pooled frequency of 97%. Pleural line abnormalities</td>
<td></td>
</tr>
<tr>
<td>are also common with a pooled frequency of 70%. While these</td>
<td></td>
</tr>
<tr>
<td>findings are not specific for COVID-19, they increase the likelihood</td>
<td></td>
</tr>
<tr>
<td>of disease in the context of a characteristic clinical presentation.</td>
<td></td>
</tr>
<tr>
<td>Other findings include consolidations, pleural thickening, and</td>
<td></td>
</tr>
<tr>
<td>pleural effusion.[550]</td>
<td></td>
</tr>
<tr>
<td>• May be used in pregnant women and children.[551] [552]</td>
<td></td>
</tr>
<tr>
<td>• Possible roles include: reducing nosocomial transmission;</td>
<td></td>
</tr>
<tr>
<td>monitoring progress of patients; and a possible role in</td>
<td></td>
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<tr>
<td>subpopulations who are vulnerable but are not suitable for CT (e.g.,</td>
<td></td>
</tr>
<tr>
<td>pregnant women).[616]</td>
<td></td>
</tr>
<tr>
<td>• [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical</td>
<td></td>
</tr>
<tr>
<td>care areas] (<a href="https://www.bsti.org.uk/media/resources/files/Lung_US">https://www.bsti.org.uk/media/resources/files/Lung_US</a></td>
<td></td>
</tr>
<tr>
<td>print_out_and_scoring_proforma.pdf)</td>
<td></td>
</tr>
<tr>
<td><strong>calprotectin</strong></td>
<td><strong>elevated</strong></td>
</tr>
<tr>
<td>• Calprotectin is an emerging biomarker of interest. Calprotectin</td>
<td></td>
</tr>
<tr>
<td>levels often increase following infection or trauma, and in</td>
<td></td>
</tr>
<tr>
<td>inflammatory disease. Serum/fecal calprotectin levels have been</td>
<td></td>
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<tr>
<td>demonstrated to be significantly elevated in COVID-19 patients with</td>
<td></td>
</tr>
<tr>
<td>severe disease, and it may have prognostic significance.[617]</td>
<td></td>
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</tbody>
</table>
### Differentials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Community-acquired pneumonia | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
  • Differentiating COVID-19 from community-acquired bacterial pneumonia is not usually possible from signs and symptoms. However, patients with bacterial pneumonia are more likely to have rapid development of symptoms and purulent sputum. They are less likely to have myalgia, anosmia, or pleuritic pain. [618] | • Blood or sputum culture or molecular testing: positive for causative organism.  
  • RT-PCR: negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA (coinfections are possible).  
  • CT chest: centrilobular nodules, mucoid impactions. [619] |
| Influenza infection         | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
  • Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.  
  • Incubation period is shorter. [620] Symptoms typically peak during the first 3 to 7 days of illness with influenza, compared with week 2 or 3 of illness with COVID-19. [621]  
  • More common in children. [621] 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. [622]  
  • Fever is less common. Rhinorrhea, sore throat, myalgia, headache, and dyspnea are more | • Only testing can distinguish between influenza infection and COVID-19 and identify coinfection. When SARS-CoV-2 and influenza viruses are cocirculating, test for both viruses in all hospitalized patients with acute respiratory illness, and only test for influenza virus in outpatients with acute respiratory illness if the results will change clinical management of the patient. [439]  
  • 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. [620]  
  • CT chest: there is emerging evidence that CT can be used for differentiating between influenza and COVID-19. COVID-19 patients are more likely to have rounded or linear opacities, crazy-paving sign, vascular enlargement, and interlobular septal |
### Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>common.[620] [623] New-onset smell and/or taste disorders were less common in a case-control study.[624]</td>
<td>thickening, but less likely to have nodules, tree-in-bud sign, bronchiectasis, and pleural effusion.[625] [626] Inflammatory markers and coagulation screen: there is emerging 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.[627]</td>
</tr>
<tr>
<td>Common cold</td>
<td>• Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.</td>
<td>• RT-PCR; positive for causative organism; negative for SARS-CoV-2 viral RNA (coinfections are possible).</td>
</tr>
<tr>
<td>Other viral or bacterial respiratory infections</td>
<td>• Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.</td>
<td>• Blood or sputum culture of molecular testing; positive for causative organism.</td>
</tr>
<tr>
<td></td>
<td>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. However, fever is less common, and headache, rhinorrhea, myalgia, and sore throat are more common. Patients may have a greater number of general symptoms.[623]</td>
<td>• RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible).</td>
</tr>
<tr>
<td></td>
<td>• Adenovirus and Mycoplasma should be considered in clusters of pneumonia patients, especially in closed settings such as military camps and schools.</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Aspiration pneumonia            | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
• Differentiating COVID-19 from 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.[628] |
| Pneumocystis jirovecii pneumonia | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
• Differentiating COVID-19 from pneumocystis jirovecii pneumonia is not usually possible from signs and symptoms.  
• Patients are usually immunocompromised (e.g., HIV positive) and duration of symptoms may be longer. | • Sputum culture: positive for Pneumocystis.  
• RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible).  
• CT chest: ground-glass opacity is usually more diffusely distributed with a tendency to spare the subpleural regions.[619] |
| Middle East respiratory syndrome (MERS) | • Travel history to the Middle East or contact with a confirmed case of MERS.  
• Differentiating COVID-19 from MERS is not possible from signs and symptoms.  
• Initial data suggest that the clinical course of COVID-19 is less severe and the case fatality rate is lower compared with MERS. | • Reverse-transcriptase polymerase chain reaction (RT-PCR): positive for MERS-CoV viral RNA. |
| Severe acute respiratory syndrome (SARS) | • There have been no cases of SARS reported since 2004. | • RT-PCR: positive for severe acute respiratory syndrome coronavirus (SARS-CoV) viral RNA. |
| Avian influenza A (H7N9) virus infection | • May be difficult to differentiate based on epidemiologic history as avian influenza H7N9 is endemic in China.  
• Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area | • RT-PCR: positive for H7-specific viral RNA. |
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<th>Condition</th>
<th>Differentiating signs / symptoms</th>
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| Avian influenza A (H5N1) virus infection       | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
• Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area when avian influenza is endemic. | • RT-PCR: positive for H5N1 viral RNA.                                                     |
| Pulmonary tuberculosis                         | • Consider diagnosis in endemic areas, especially in patients who are immunocompromised.        | • 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 Mycoplasma tuberculosis. | |
| Febrile neutropenia                            | • Suspect neutropenic sepsis in patients with a history of recent systemic anticancer treatment who present with fever (with or without respiratory symptoms) as this can be rapid and life-threatening.[629]  
• Symptoms of COVID-19 and neutropenic sepsis may be difficult to differentiate at initial presentation. | • CBC: neutropenia.  
• RT-PCR: negative for SARS-CoV-2 viral RNA.                                               |

## Criteria

### Case definitions

Various case definitions are available:


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Screening

Management of contacts

Definition

- The World Health Organization defines a contact as a person who has experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:[630]
  - Face-to-face contact with a probable or confirmed case within 3 feet (1 meter) and for more than 15 minutes
  - Direct physical contact with a probable or confirmed case
  - Direct care for a patient with probable or confirmed COVID-19 without using recommended personal protective equipment
  - Other situations as indicated by local risk assessments.

- The Centers for Disease Control and Prevention (CDC) defines a close contact as someone who has been within 6 feet (2 meters) of an infected person for at least 15 minutes over a 24-hour period, beginning 2 days before symptom onset (or 2 days before testing in asymptomatic patients).[191]
- Consult local guidance as definitions of a contact may vary depending on local public health advice.

Quarantine periods

- Contacts should remain in quarantine and monitor their health for up to 14 days from the last day of possible contact with the infected person.
- In the UK, Public Health England recommends a 10-day quarantine (or self-isolation) period after a potential exposure (it was reduced from 14 days to 10 days on 14 December 2020).[631]
- The CDC has shortened the minimum quarantine time after a potential exposure from 14 days to 7-10 days. Quarantine can end after day 7 if the patient tests negative and no symptoms have been reported during the quarantine period. Quarantine can end after day 10 without testing and if no symptoms have been reported during the quarantine period. Additional criteria (e.g., symptom monitoring, mask wearing) should continue until day 14 in both cases.[632]
- Consult local guidance for recommended quarantine locations and timeframes as recommendations vary depending on local public health advice.

Screening of travelers

Exit and entry screening may be recommended in countries where borders are still open, particularly when repatriating nationals from affected areas. Travelers returning from affected areas should self-monitor for symptoms for 14 days and follow local protocols of the receiving country. Some countries may require travelers to enter mandatory quarantine in a designated location (e.g., a hotel). Travelers who develop symptoms are advised to contact their local healthcare provider, preferably by phone.[633] One study of 566 repatriated Japanese nationals from Wuhan City found that symptom-based screening performed poorly and missed presymptomatic and asymptomatic cases. This highlights the need for testing and follow-up.[634]
**Drive-through screening centers**

Drive-through screening centers have been set up in some countries for safer and more efficient screening. The testee does not leave their car throughout the entire process, which includes registration and questionnaire, exam, specimen collection, and instructions on what to do after. This method has the advantage of increased testing capacity and prevention of cross-infection between testees in the waiting space.[635]

**Temperature screening**

There is little scientific evidence to support temperature screening with thermal cameras or temperature screening products as a reliable method for the detection of COVID-19 or any other febrile illness, especially if used as the main method of testing.[636]

Noncontact infrared thermometers generally have reasonable sensitivity and specificity for detecting fever; however, their performance varies in different settings. Environmental factors (e.g., absolute temperature, variation in temperature, relative humidity) play an important role in the accuracy of the result. False negatives may be seen in people wearing make-up on the target area or who are significantly perspiring. False positives may be seen in people who are pregnant, menstruating, or on hormone replacement therapy, or those who have recently consumed alcohol or hot beverages, or done strenuous physical activity. Also, fever is not present in asymptomatic or presymptomatic people, and may not be present in symptomatic people, which means infected individuals could be missed.[637]

While the forehead is the most feasible site for scanning, it is thought to be more prone to physiologic and environmental variations, and the wrist may be a better option as it may give more stable measurements under different circumstances.[638]

Noncontact infrared thermometers demonstrated variable accuracy levels across populations and had a low sensitivity for temperatures >99.5°F (>37.5°C) in adults compared with temporal artery thermometers. Therefore, they may not be the most accurate device for the mass screening of fever during a pandemic.[639]
Approach

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

Best Practice has published a separate topic on the management of coexisting conditions in the context of COVID-19. [BMJ Best Practice: Management of coexisting conditions in the context of COVID-19] (https://bestpractice.bmj.com/topics/en-us/3000190#important-update)

Key recommendations

- Consider whether the patient can be managed at home. Generally, patients with asymptomatic or mild disease can be managed at home or in a community facility.[136]
- Admit patients with moderate or severe disease to an appropriate healthcare facility. Assess adults for frailty on admission. Patients with critical disease require intensive care; involve the critical care team in discussions about admission to critical care when necessary. Monitor patients closely for signs of disease progression.[136] [478]
- Provide symptom relief as necessary. This may include treatments for fever, cough, breathlessness, anxiety, delirium, or agitation.[136] [478]
- Start supportive care according to the clinical presentation. This might include oxygen therapy, intravenous fluids, venous thromboembolism prophylaxis, high-flow nasal oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. Sepsis and septic shock should be managed according to local protocols.[136]
- Consider empiric antibiotics if there is clinical suspicion of a secondary bacterial infection. Antibiotics may be required in patients with moderate, severe, or critical disease. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria. Base the regimen on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.[136] [478]
- Consider systemic corticosteroid therapy for 7 to 10 days in adults with severe or critical disease. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe and critical disease, and probably reduce the need for invasive ventilation.[439] [652]
- Assess whether the patient requires any rehabilitation or follow-up after discharge. Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[136]
- For full details and guidance see information below.

Location of care

The decision about location of care depends on various factors including clinical presentation, disease severity, need for supportive care, presence of risk factors for severe disease, and conditions at home (including the presence of vulnerable people). Make the decision on a case-by-case basis using the following general principles.[136]

- Mild disease: manage in a healthcare facility, in a community facility, or at home. Home isolation can be considered in most patients, including asymptomatic patients.
• Moderate disease: manage in a healthcare facility, in a community facility, or at home. Home isolation can be considered in low-risk patients (i.e., patients who are not at high risk of deterioration).
• Severe disease: manage in an appropriate healthcare facility.
• Critical disease: manage in an intensive/critical care unit.

The location of care will also depend on guidance from local health authorities and available resources. Forced quarantine orders are being used in some countries.

Manage people who require hospitalization and who are at risk of being infected with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant of concern in a single room with en-suite bathroom facilities and appropriate infection control procedures for the duration of their isolation period. In those who test positive, discuss further risk assessment and appropriate case management with the local/regional specialist infectious diseases center.[192]

The strongest risk factors for hospital admission are older age (odds ratio of >2 for all age groups older than 44 years, and odds ratio of 37.9 for people ages 75 years and over), heart failure, male sex, chronic kidney disease, and increased body mass index (BMI).[653] The median time from onset of symptoms to hospital admission is around 7 days.[49] [557]

Children are less likely to require hospitalization, but, if admitted, generally only require supportive care.[21] [654] Risk factors for intensive care admission in children include age <1 month, male sex, preexisting medical conditions, and presence of lower respiratory tract infection signs or symptoms at presentation.[655] The majority of children who require ventilation have underlying comorbidities, most commonly cardiac disease.[656] Children with COVID-19 are reported to have similar hospitalization rates, intensive care admission rates, and mechanical ventilator use compared with those with seasonal influenza.[622]

Overall, 19% of hospitalized patients require noninvasive ventilation, 17% require intensive care, 9% require invasive ventilation, and 2% require extracorporeal membrane oxygenation.[558] The rate of intensive care admission varies between studies; however, a meta-analysis of nearly 25,000 patients found that the admission rate was 32%, and the pooled prevalence of mortality in patients in the intensive care unit was 39%.[657] Another more recent meta-analysis found the mortality rate in patients in the intensive care unit to be 35.5%.[658] The most common reasons for intensive care unit admission are hypoxemic respiratory failure leading to mechanical ventilation and hypotension.[659] Patients admitted to intensive care units were older, were predominantly male, and had a median length of stay of 23 days (range 12 to 32 days).[660] The strongest risk factors for critical illness are oxygen saturation <88%; elevated serum troponin, C-reactive protein, and D-dimer; and, to a lesser extent, older age, BMI >40, heart failure, and male sex.[653] The most common risk factors for intensive care unit mortality were invasive mechanical ventilation, acute kidney injury, and acute respiratory distress syndrome.[661]

**Management of mild COVID-19**

Patients with suspected or confirmed mild disease (i.e., symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia) and asymptomatic patients should be isolated to contain virus transmission.[136]

Location of care
• Manage patients in a healthcare facility, in a community facility, or at home. Home isolation can be considered in most patients, with telemedicine or remote visits as appropriate.[136] [439] This decision requires careful clinical judgment and should be informed by an assessment of the patient's home environment to ensure that: infection prevention and control measures and other requirements can be met (e.g., basic hygiene, adequate ventilation); the caregiver is able to provide care and recognize when the patient may be deteriorating; the caregiver has adequate support (e.g., food, supplies, psychological support); the support of a trained health worker is available in the community.[630]

Isolation period

• Discontinue transmission-based precautions (including isolation) and release patients from the care pathway: 10 days after positive test (asymptomatic patients); 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms (symptomatic patients).[136]
• The Centers for Disease Control and Prevention (CDC) recommends discontinuing home isolation once at least 10 days (or up to 20 days in patients who are severely immunocompromised) have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. In asymptomatic people, the CDC recommends discontinuing home isolation once at least 10 days have passed since the date of a positive test. For severely immunocompromised patients who are asymptomatic, isolation may be discontinued when at least 10 days and up to 20 days have passed since the date of a positive test; consider consultation with infectious diseases specialists and infection control experts. Alternatively, the CDC recommends at least two negative reverse-transcription polymerase chain reaction (RT-PCR) tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[662] If the patient is hospitalized, the CDC guidance for discontinuing isolation is the same as for moderate disease (see below).
• Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the self-isolation period is 10 days in patients with milder disease who are managed in the community.[663]

Infection prevention and control

• For patients in home isolation, advise patients and household members to follow appropriate infection prevention and control measures:

Symptom management

• Fever and pain: acetaminophen or ibuprofen are recommended.[136] [478] There is no evidence at present of severe adverse events in COVID-19 patients taking nonsteroidal anti-inflammatory drugs
Coronavirus disease 2019 (COVID-19) Management

(NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilization, long-term survival, or quality of life in patients with COVID-19.[664] [665] [666] [667] [668] [669] [670] Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms.

• Cough: advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough.[478] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[671]

• Olfactory dysfunction: consider treatment (e.g., olfactory training) if olfactory dysfunction persists beyond 2 weeks. Often it improves spontaneously and does not require specific treatment. There is no evidence to support the use of treatments in patients with COVID-19.[672]

Supportive care

• Advise patients about adequate nutrition and appropriate rehydration. Advise patients to drink fluids regularly to avoid dehydration. Fluid intake needs can be higher than usual because of fever. However, too much fluid can worsen oxygenation.[136] [478]

• Advise patients to improve air circulation by opening a window or door.[478]

• Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[136]

Monitor

• Closely monitor patients with risk factors for severe illness, and counsel patients about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain).[136] [439]

• 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.[136]

Management of moderate COVID-19

Patients with suspected or confirmed moderate disease (i.e., clinical signs of pneumonia but no signs of severe pneumonia) should be isolated to contain virus transmission.[136]

Location of care

• Manage patients in a healthcare facility, in a community facility, or at home. Home isolation, with telemedicine or remote visits as appropriate, can be considered in low-risk patients. Manage patients at high risk of deterioration in a healthcare facility.[136] [439]

Isolation period

• Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[136]

• The CDC recommends discontinuing isolation once at least 10 days (not severely immunocompromised) or up to 20 days (severely immunocompromised) have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. In asymptomatic
people, the CDC recommends discontinuing isolation once at least 10 days (not severely immunocompromised) or up to 20 days (severely immunocompromised) have passed since the date of a positive test. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative RT-PCR tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[673] If the patient is isolated at home, the CDC guidance for discontinuing isolation is the same as for mild disease (see above).

• Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients, and 10 days in patients with milder disease who are managed in the community. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[663]

Infection prevention and control

• Implement local infection prevention and control procedures when managing patients with COVID-19. For patients in home isolation, advise patients and household members to follow appropriate infection prevention and control measures (see above).

Symptom management and supportive care

• Manage symptoms and provide supportive care as appropriate (see above).

Antibiotics

• Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.[478]

• Consider empiric antibiotics only if there is clinical suspicion of secondary bacterial infection. Start treatment as soon as possible, and refer to local guidelines for choice of regimen.[136] [439] [478]

• Antibiotics may also be considered in older people (particularly those in long-term care facilities) and children <5 years of age to provide empiric antibiotic treatment for possible pneumonia.[136]

• 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.[478]

Monitor

• Closely monitor patients for signs or symptoms of disease progression.

• If the patient is being managed at home, counsel them about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain). Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalized. Patient education and appropriate follow-up are required.[136]
• If the patient is being managed in hospital, monitor patients closely for signs of clinical deterioration using medical early warning scores (e.g., National Early Warning Score 2 [NEWS2]), and respond immediately with appropriate supportive care interventions.\[136\]

Corticosteroids

• The WHO does not recommend corticosteroids in patients with nonsevere disease as they may increase the risk of mortality in these patients.\[652\] In the UK, NHS England supports these guidelines, and does not recommend the use of corticosteroids in patients with nonsevere COVID-19.\[674\] In the US, the National Institutes of Health guidelines panel recommends against the use of corticosteroids in nonhospitalized patients with mild to moderate disease.\[439\]

Management of severe COVID-19

Patients with suspected or confirmed severe disease are at risk of rapid clinical deterioration.\[136\]

• Severe disease in adults is defined as having clinical signs of pneumonia plus at least one of the following:
  • Respiratory rate >30 breaths/minute
  • Severe respiratory distress
  • SpO₂ <90% on room air

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

Location of care

• Manage patients in an appropriate healthcare facility under the guidance of a specialist team.\[136\]
• Use the Clinical Frailty Scale (CFS) to assess baseline health and inform discussions on treatment expectations when appropriate and within an individualised assessment of frailty. [Clinical Frailty Scale] (https://www.scfn.org.uk/clinical-frailty-scale) Do not use the CFS for younger people, or for people with stable long-term disabilities (e.g., cerebral palsy), learning disabilities, or autism. Make an individualized assessment of frailty in these people, using clinical assessment and alternative scoring methods.\[478\]
  • A meta-analysis found that an increase in CFS was associated with an increase in mortality (each 1-point increase in CFS was associated with a 12% increase in mortality).\[675\] However, some studies suggest that a more nuanced understanding of frailty and outcomes is needed, and you should exercise caution in placing too much emphasis on the influence of frailty alone when discussing prognosis in older people.\[676\]

Isolation period

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• Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[136]

• The CDC recommends discontinuing isolation once at least 10 days and up to 20 days have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. Consider consultation with infection control experts before discontinuing isolation. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative RT-PCR tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[673]

• Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[663]

Infection prevention and control

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

Oxygen

• Start supplemental oxygen therapy immediately in any patient with emergency signs (i.e., obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions), or any patient without emergency signs and SpO₂ <90%.[136] [439] There is no evidence of benefit for oxygen therapy in patients with COVID-19 in the absence of hypoxemia.[677]

• Target SpO₂ to ≥94% during resuscitation in adults and children with emergency signs who require emergency airway management and oxygen therapy. Once the patient is stable, a target SpO₂ >90% in children and nonpregnant adults, and ≥92% to 95% in pregnant women is recommended. Nasal prongs or a nasal cannula are preferred in young children.[136] Some guidelines recommend that SpO₂ should be maintained no higher than 96%.[678]

• Some centers may recommend different SpO₂ targets in order to support prioritization of oxygen flow for the most severely ill patients in hospital. NHS England recommends a target of 92% to 96% (or 90% to 94% if clinically appropriate), for example.[679]

• Consider positioning techniques (e.g., high supported sitting), and airway clearance management to optimize oxygenation and assist with secretion clearance in adults. Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require supplemental oxygen.[136] [439] Early self-proning of awake, nonintubated patients has been shown to improve oxygen saturation and may delay or reduce the need for intensive care.[680] [681] [682] [683] [684]

• Monitor patients closely for signs of progressive acute hypoxemic respiratory failure. Patients who continue to deteriorate despite standard oxygen therapy require advanced oxygen/ventilatory support.[136] [439]
Symptom management and supportive care

- Fluids and electrolytes: use cautious fluid management in adults and children without tissue hypoperfusion and fluid responsiveness as aggressive fluid resuscitation may worsen oxygenation.[136] Correct any electrolyte or metabolic abnormalities, such as hyperglycemia or metabolic acidosis, according to local protocols.[685]

- Fever and pain: acetaminophen or ibuprofen are recommended.[136] [478] There is no evidence at present of severe adverse events in COVID-19 patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilization, long-term survival, or quality of life in patients with COVID-19.[664] [665] [666] [667] [668] [669] [670] Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms.

- Cough: advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough. Short-term use of a cough suppressant may be considered in select patients (e.g., if the cough is distressing to the patient) provided there are no contraindications.[478] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[671]

- 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).[478]

- Anxiety, delirium, and agitation: identify and treat any underlying or reversible causes (e.g., offer reassurance, treat hypoxia, correct metabolic or endocrine abnormalities, address coinfections, minimize use of drugs that may cause or worsen delirium, treat substance withdrawal, maintain normal sleep cycles, treat pain or breathlessness).[136] [478] Low doses of haloperidol (or another suitable antipsychotic) can also be considered for agitation.[136] Nonpharmacologic interventions are the mainstay for the management of delirium when possible, and prevention is key.[686]

- 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.[687]

- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia or depression as appropriate.[136]

Venous thromboembolism prophylaxis

- Assess the risk of bleeding as soon as possible after admission, or by the time of the first consultant review, using a suitable risk assessment tool.[478]

- Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalized adults and adolescents, provided there are no contraindications.[136] [439] [688] [689]

  - The National Institute for Health and Care Excellence in the UK recommends starting as soon as possible and within 14 hours of admission, and continuing for a minimum of 14 days or until discharge.[478]

  - For hospitalized children, indications for VTE prophylaxis should be the same as those for children without COVID-19.[439]

- Low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options for standard thromboprophylaxis.[136]
Coronavirus disease 2019 (COVID-19)

Management

• The National Institute for Health and Care Excellence in the UK recommends low molecular weight heparin first-line, with fondaparinux or unfractionated heparin reserved for patients who cannot have low molecular weight heparin.[478]

• A retrospective observational study found that enoxaparin is associated with lower 28-day mortality, lower rates of bleeding events, lower intensive care admission rates, and shorter hospital stays compared with unfractionated heparin; however, the study had important limitations and further research is required.[690]

• Unfractionated heparin is contraindicated in patients with severe thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia. Mechanical thromboprophylaxis (e.g., intermittent pneumatic compression devices) is recommended if anticoagulation is contraindicated or not available.[689] [691]

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

• The World Health Organization recommends standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing in patients without an established indication for higher-dose anticoagulation.[136]

• The National Institute for Health and Care Excellence in the UK recommends clinicians consider a treatment dose of a low molecular weight heparin in young people and adults who are likely to be in hospital for at least 3 days and need supplemental oxygen (but who are not yet receiving high-flow oxygen, continuous positive airway pressure, noninvasive ventilation, or invasive mechanical ventilation), unless contraindicated. This is because of fewer deaths and less likelihood of needing intensive care with this dose compared with a standard prophylaxis dose without a notable increase in major bleeding, although the evidence for this recommendation is weak. Treatment should be for a minimum of 14 days or until discharge, and the dose may need to be reduced if the clinical circumstances change (such as a need for advanced respiratory support). For those who do not need supplemental oxygen, follow standard VTE prophylaxis guidelines.[478]

• The National Institutes of Health guidelines panel recommends prophylactic-dose anticoagulation, and states that there are insufficient data to recommend increased anticoagulant doses for VTE prophylaxis in COVID-19 patients outside the setting of a clinical trial.[439]

• Dose adjustments may be required in patients with extremes of body weight or renal impairment.[478]

• For patients who are already on an anticoagulant for another condition, continue the patient’s current therapeutic dose unless contraindicated by a change in clinical circumstances. 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.[478]

• Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected.[136] If the patient’s clinical condition changes, assess the risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.[478]

• Continue until hospital discharge.[136] Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients.[439] [688] [689] Ensure patients who require
VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.[478]

• There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulation in hospitalized patients with COVID-19.[692]

  • A retrospective analysis of over 4000 patients found that anticoagulation was associated with lower mortality and intubation among hospitalized COVID-19 patients. Therapeutic anticoagulation was associated with lower mortality compared with prophylactic anticoagulation, but the difference was not statistically significant.[693]
  • An observational cohort study of over 4000 patients found that early initiation of prophylactic anticoagulation in hospitalized patients was associated with a decreased risk of 30-day mortality and no increased risk of serious bleeding events compared with no anticoagulation.[694]
  • Clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[688]

Antimicrobials

• 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.[478] There is insufficient evidence to recommend empiric broad-spectrum antibiotics in the absence of another indication.[439]

• Consider empiric antibiotics if there is clinical suspicion of secondary bacterial infection. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria (or within 4 hours of establishing a diagnosis of secondary bacterial pneumonia); do not wait for microbiology results. Base the regimen on the clinical diagnosis (e.g., community-acquired pneumonia, hospital-acquired pneumonia, sepsis), local epidemiology and susceptibility data, and local treatment guidelines.[136] [439] [478]

• Consider seeking specialist advice for people who: are immunocompromised; have a history of infection with resistant organisms; have a history of repeated infective exacerbations of lung disease; are pregnant; or are receiving advanced respiratory or organ support. Seek specialist advice if there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic, or there is clinical or microbiologic evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.[478]

• Reassess antibiotic use daily. De-escalate empiric therapy on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching from intravenous to oral therapy. Duration of treatment should be as short as possible (e.g., 5 to 7 days). Antibiotic stewardship programs should be in place.[136] 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.[695]

• Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.[136] The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection. Start empiric treatment with oseltamivir in hospitalized patients who are suspected of having either or both infections as soon as possible without waiting for influenza test results. Antiviral therapy can be stopped once influenza has been ruled out.[439]

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 or critical disease. This recommendation is based on two meta-analyses that pooled data from eight randomized trials (over 7000 patients), including the UK RECOVERY trial. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe and critical disease. They also probably reduce the need for invasive ventilation. There is no evidence directly comparing dexamethasone and hydrocortisone. The harms of treatment in this context are considered to be minor. It is unclear whether these recommendations can be applied to children or those who are immunocompromised. The WHO does not recommend corticosteroids in patients with nonsevere disease as they may increase the risk of mortality in these patients.[652] [696] [697] [698] There is also evidence that corticosteroids probably reduce the length of intensive care unit stay (low certainty), and increase ventilator-free days (moderate certainty).[699] [700]

• In Europe, the European Medicines Agency has endorsed the use of dexamethasone for patients with severe disease who require oxygen therapy or mechanical ventilation.[701]

• In the US, the National Institutes of Health guidelines panel recommends dexamethasone, either alone or in combination with remdesivir (see the Emerging section for information on remdesivir), in hospitalized patients who require supplemental oxygen. The panel recommends against using dexamethasone in patients who do not require supplemental oxygen. Alternative corticosteroids may be used in situations where dexamethasone is not available.[439] The Infectious Diseases Society of America supports the use of dexamethasone in hospitalized patients with severe disease.[702]

• Monitor patients for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.[439]

• Inhaled corticosteroids (e.g., budesonide) are also undergoing clinical trials.[703]

Monitor

• Monitor patients closely for signs of clinical deterioration, and respond immediately with appropriate supportive care interventions.[136]

Discharge and rehabilitation

• Routinely assess older patients for mobility, functional swallow, cognitive impairment, and mental health concerns, and based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[136]

Palliative care

• Palliative care interventions should be made accessible at each institution that provides care for patients with COVID-19. Identify whether the patient has an advance care plan and respect the patient’s priorities and preferences when formulating the patient’s care plan.[136] Follow local palliative care guidelines.

Management of critical COVID-19

Patients with critical disease (i.e., presence of acute respiratory distress syndrome, sepsis, or septic shock) should be admitted or transferred to an intensive/critical care unit. Use existing care bundles (i.e., three or more evidence-informed practices delivered together and consistently to improve care), chosen locally by the hospital or intensive care unit and adapted as necessary for local circumstances.[136]
Coronavirus disease 2019 (COVID-19) Management

Location of care

- Manage patients in an intensive/critical care unit under the guidance of a specialist team.\[136\]
- Discuss the risks, benefits, and potential outcomes of treatment options with patients and their families, and allow them to express preferences about their management. Take their wishes and expectations into account when considering the ceiling of treatment. Use decision support tools if available. Put treatment escalation plans in place, and discuss any existing advance care plans or advance decisions to refuse treatment with patients who have preexisting advanced comorbidities.\[478\]

Isolation period

- Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.\[136\]
- The CDC recommends discontinuing isolation once at least 10 days and up to 20 days have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. Consider consultation with infection control experts before discontinuing isolation. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative RT-PCR tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.\[673\]
- Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.\[663\]

Infection prevention and control

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

High-flow nasal oxygen or noninvasive ventilation

- Consider a trial of high-flow nasal oxygen (HFNO) or noninvasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in selected patients with mild acute respiratory distress syndrome (ARDS). Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require HFNO or noninvasive ventilation.\[136\]
- Airborne precautions are recommended for these interventions (including bubble CPAP) due to uncertainty about the potential for aerosolization.\[136\] Novel methods to protect clinicians without access to standard personal protective equipment during aerosol-generating procedures have been suggested.\[704\] [705] [706] [707]
- Patients with hypercapnia, hemodynamic instability, multi-organ failure, or abnormal mental status should generally not receive HFNO, although emerging data suggests that it may be safe in patients with mild to moderate and nonworsening hypercapnia. Patients with hypoxemic respiratory
failure and hemodynamic instability, multi-organ failure, or abnormal mental status should not receive these treatments in place of other options such as invasive ventilation.[136]

• There is an ongoing debate about the optimal mode of respiratory support before mechanical ventilation.[708] NHS England recommends CPAP as the preferred form of noninvasive ventilation in patients with hypoxic (type 1) respiratory failure. It doesn't advocate the use of HFNO based on a lack of efficacy, oxygen use (HFNO can place a strain on oxygen supplies with the risk of site supply failure), and infection spread.[709] Other guidelines recommend HFNO over noninvasive ventilation, unless HFNO is not available.[439] [678] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[710]

• Early CPAP may provide a bridge to invasive mechanical ventilation. Reserve the use of BiPAP for patients with hypercapnic acute on chronic ventilatory failure (type 2 respiratory failure).[709]

• Indirect and low-certainty evidence suggests that noninvasive ventilation probably reduces mortality in patients with COVID-19, similar to mechanical ventilation, but may increase the risk of viral transmission.[711] [712]

• Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions they require urgent endotracheal intubation.[136] [678]

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

Mechanical ventilation

• Consider endotracheal intubation and invasive mechanical ventilation in patients who are acutely deteriorating despite advanced oxygen/noninvasive ventilatory support measures.[136] [439]

• Two-thirds of patients who required critical care in the UK had mechanical ventilation within 24 hours of admission.[713] In New York, 33% of hospitalized patients developed respiratory failure leading to mechanical ventilation. These patients were more likely to be male, have obesity, and have elevated inflammatory markers and liver function tests.[454] Patients spent an average of 18 days on a ventilator (range 9-28 days).[714] Patients who required invasive mechanical ventilation had an 36% to 88% mortality rate in studies.[715] [716] [717]

• Endotracheal intubation should be performed by an experienced provider using airborne precautions.[136] Intubation by video laryngoscopy is recommended if possible.[439] Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require preoxygenation with 100% FiO₂ for 5 minutes.[136]

• Mechanically ventilated patients with ARDS should receive a lung-protective, low tidal volume/low inspiratory pressure ventilation strategy (lower targets are recommended in children). A higher positive end-expiratory pressure (PEEP) strategy is preferred over a lower PEEP strategy in moderate to severe ARDS. However, individualization of PEEP, where the patient is monitored for beneficial or harmful effects and driving pressure during titration with consideration of the risks and benefits of PEEP titration, is recommended.[136] [439] [678] NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[718]

• Although some patients with COVID-19 pneumonia meet the criteria for ARDS, there is some discussion about whether COVID-19 pneumonia is its own specific disease with atypical phenotypes. Anecdotal evidence suggests that the main characteristic of the atypical presentation is the dissociation between well-preserved lung mechanics and the severity of hypoxemia.[719] [720] [721] [722] [723] [724] However, this approach has been criticized.[725] [726] 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.[727] As a consequence of this, some clinicians have warned that protocol-driven ventilator use may be causing lung
injury in some patients, and that ventilator settings should be based on physiologic findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.[719] PEEP should always be carefully titrated.[728]

- 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.[136] [439] [678] Longer durations may be feasible in some patients.[729] A small cohort study of 12 patients in Wuhan City, China, with COVID-19-related ARDS suggests that spending periods of time in the prone position may improve lung recruitability.[730] Two small case series found that many people tolerate the prone position while awake, breathing spontaneously, or receiving noninvasive ventilation. In the patients who tolerated it, improvement in oxygenation and a decrease in respiratory rate occurred.[731] [732]

- Lung recruitment maneuvers are suggested, but staircase recruitment maneuvers are not recommended.[439] [678]

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

Inhaled pulmonary vasodilator

- Consider a trial of an inhaled pulmonary vasodilator in adults who have severe ARDS and hypoxemia despite optimizing ventilation. Taper off if there is no rapid improvement in oxygenation.[439] [678]

Extracorporeal membrane oxygenation

- Consider extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[136] [678] [733] [734] ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[735]

- There is insufficient evidence to recommend either for or against the routine use of ECMO.[439]

- The estimated 60-day survival rate of ECMO-rescued patients with COVID-19 (31%) was similar to that of previous studies of ECMO for severe ARDS.[736] An international cohort study of 1035 patients found that both the estimated mortality 90 days after ECMO initiation and mortality in those who achieved a final outcome of death or discharge were <40%, consistent with previously reported survival rates in acute hypoxemic respiratory failure.[737]

- Single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure.[738]

Management of septic shock/sepsis

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

Symptom management and supportive care

- Consider fluid and electrolyte management, antimicrobial treatment, VTE prophylaxis, and symptom management as appropriate (see above).

- For VTE prophylaxis, unfractionated heparin is preferred over fondaparinux in critically ill patients if low molecular weight heparin cannot be used.[689]
• The UK National Institute for Health and Care Excellence (NICE) does not recommend treatment-dose low molecular weight heparin for VTE prophylaxis for patients receiving advanced respiratory support unless the patient is part of a nationally approved clinical trial because it is likely to cause harm in this group. NICE recommends reducing the dose to a locally agreed intermediate or standard dose and reassessing VTE and bleeding risks daily in patients who progress to needing high-flow oxygen, continuous positive airway pressure, noninvasive or invasive mechanical ventilation, or palliative care. [478]

• NHS England recommends that therapeutic doses should not be offered unless there is a standard indication for therapeutic anticoagulation, as trials show that therapeutic doses do not improve clinical outcome of severe disease in the critical care setting. [739]

• Some guidelines recommend that escalated doses can be considered in critically ill patients. [688] [740]

• A multicenter randomized controlled trial found that intermediate-dose prophylactic anticoagulation did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or 30-day mortality compared with standard-dose prophylactic anticoagulation among patients admitted to the intensive care unit. These results do not support the routine empiric use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the intensive care unit. [741]

Corticosteroids

• Consider systemic corticosteroids for the management of critically ill patients (see above). In the US, the National Institutes of Health guidelines panel recommends dexamethasone, either alone or in combination with remdesivir, in hospitalized patients who require high-flow oxygen or noninvasive ventilation. The panel recommends dexamethasone alone in patients on mechanical ventilation or ECMO. [439]

• A meta-analysis found an increased risk of VTE with corticosteroid administration in patients with critical disease. However, no definite findings were available due to the differing corticosteroid regimens and the heterogeneity of the studies. [742]

Discharge and rehabilitation

• Routinely assess intensive care patients for mobility, functional swallow, cognitive impairment, and mental health concerns, and based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements. [136]

Palliative care

• Palliative care interventions should be made accessible at each institution that provides care for patients with COVID-19. Identify whether the patient has an advance care plan and respect the patient’s priorities and preferences when formulating the patient’s care plan. [136] Follow local palliative care guidelines.

Management of pregnant women

Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as midwifery and mental health and psychosocial support. A woman-centered, respectful, skilled approach to care is recommended. [136] In women with severe
or critical disease, the multidisciplinary team should be organized as soon as possible after maternal hypoxemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery. [743]

There are limited data available on the management of pregnant women with COVID-19; however, pregnant women can generally be treated with the same supportive therapies detailed above, taking into account the physiologic changes that occur with pregnancy. [136]

The prevalence of asymptomatic SARS-CoV-2-positive pregnant women admitted for delivery appears to be low (<3% in a cohort in Connecticut, and 0.43% in a cohort in California). [744] [745] Screening women and their delivery partners before admission may not be helpful. More than 15% of asymptomatic maternity patients tested positive for SARS-CoV-2 infection despite having been screened negative using a telephone screening tool in one small observational study in New York. In addition to this, 58% of their asymptomatic support persons tested positive despite being screened negative. [746] Another study in a New York obstetric population found that 88% of women who tested positive for SARS-CoV-2 at admission were asymptomatic at presentation. [747]

Location of care

- Manage pregnant women in a healthcare facility, in a community facility, or at home. Women with suspected or confirmed mild disease may not require acute care in a hospital unless there is concern for rapid deterioration or an inability to return to hospital promptly. [136] Follow local infection prevention and control procedures as for nonpregnant people.
- Consider home care in women with asymptomatic or mild illness, provided the patient has no signs of potentially severe illness (e.g., breathlessness, hemoptysis, new chest pain/pressure, anorexia, dehydration, confusion), no comorbidities, and no obstetric issues; the patient is able to care for herself; and monitoring and follow-up is possible. Otherwise, manage pregnant women in a hospital setting with appropriate maternal and fetal monitoring whenever possible. [528] [748] [749]
- Postpone routine prenatal or postpartum health visits for women who are in home isolation and reschedule them after the isolation period is completed. Delivery of counseling and care should be conducted via telemedicine whenever possible. Counsel women about healthy diet, mobility and exercise, intake of micronutrients, smoking, and alcohol and substance use. Advise women to seek urgent care if they develop any worsening of illness or danger signs, or danger signs of pregnancy. [136]

Prenatal corticosteroids

- Consider prenatal corticosteroids for fetal lung maturation in women who are at risk of preterm birth (24 to 37 weeks’ gestation). Caution is advised because corticosteroids could potentially worsen the maternal clinical condition, and the decision should be made in conjunction with the multidisciplinary team. [528] [749] [750] The WHO recommends prenatal corticosteroids only when there is no clinical evidence of maternal infection and adequate childbirth and newborn care is available, and in women with mild COVID-19 after assessing the risks and benefits. [136]
There is no evidence that corticosteroids in the doses prescribed for fetal lung maturation cause any harm in the context of COVID-19, but there is also no evidence of safety. The unknown effect on maternal outcome should be weighed against the neonatal benefit, particularly at later preterm gestations.[751]

Treatments

Most clinical trials to date have excluded pregnant women. However, potentially effective treatments should not be withheld from pregnant women due to theoretical concerns about the safety of these therapeutic agents in pregnancy. Decisions should be made with a shared decision-making process between the patient and the clinical team.[439]

VTE prophylaxis

The National Institutes of Health recommends prophylactic dose anticoagulation in pregnant women who are hospitalized with severe disease, provided there are no contraindications to its use. Anticoagulation during labor and delivery requires specialized care and planning, and should be managed in a similar way to pregnant women with other conditions that require anticoagulation. VTE prophylaxis after discharge is not recommended.[439]

The Royal College of Obstetricians and Gynaecologists (RCOG) has also published guidance on the prevention of VTE in pregnant women.[751]

Labor and delivery

Implement local infection prevention and control measures during labor and delivery. Screen birth partners for COVID-19 infection using the standard case definition.[136]

Individualize mode of birth based on obstetric indications and the woman’s preferences. Vaginal delivery is preferred in women with confirmed infection to avoid unnecessary surgical complications. Induction of labor, interventions to accelerate labor and delivery, and cesarean delivery are generally only recommended when medically justified based on maternal and fetal condition. COVID-19 positive status alone is not an indication for cesarean section.[136] [528] [749]

Delayed umbilical cord clamping (not earlier than 1 minute after birth) is recommended for improved maternal and infant health and nutrition outcomes. The risk of transmission via blood is thought to be minimal, and there is no evidence that delayed cord clamping increases the risk of viral transmission from the mother to the newborn.[136]

Consider babies born to mothers with suspected or confirmed infection to be a person under investigation and isolate them from healthy newborns. Test them for infection 24 hours after birth, and again 48 hours after birth.[752]

Newborn care

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

A retrospective cohort analysis, the largest series to date, found no clinical evidence of vertical transmission in 101 newborns born to mothers with suspected or confirmed SARS-CoV-2 infection, despite most newborns rooming-in and direct breastfeeding practices. This suggests that separation may not be warranted and breastfeeding appears to be safe.[753]

The WHO recommends that mothers and infants should remain together unless the mother is too sick to care for her baby. Breastfeeding should be encouraged while applying appropriate
infection prevention and control measures (e.g., performing hand hygiene before and after contact with the baby, wearing a mask while breastfeeding).[136] The WHO advises that the benefits of breastfeeding outweigh the potential risks for transmission.[754] Mother-to-infant transmission appears to be rare during rooming-in, provided that adequate droplet and contact precautions are taken.[755]

- The CDC recommends that temporary separation of a newborn from a mother with confirmed or suspected COVID-19 may be considered after weighing the risks and benefits as current evidence suggests the risk of a neonate acquiring infection from its mother is low; healthcare providers should respect maternal autonomy in the medical decision-making process. If separation is not undertaken, measures to minimize the risk of transmission should be implemented.[756] A mother with confirmed infection should be counseled to take all possible precautions to avoid transmission to the infant during breastfeeding (e.g., hand hygiene, wearing a cloth face covering). Expressed milk should be fed to the newborn by a healthy caregiver.[757]

- The RCOG recommends that mothers with confirmed infection and healthy babies are kept together in the immediate postpartum period. It is recommended that the risks and benefits are discussed with neonatologists and families in order to individualize care in babies who may be more susceptible to infection. The RCOG advises that the benefits of breastfeeding outweigh any potential risks of transmission of the virus through breast milk, and recommends appropriate preventive precautions to limit transmission to the baby.[751]

- The American Academy of Pediatrics (AAP) recommends that mothers and newborns may room-in, with appropriate infection prevention and control precautions, according to usual center practice. However, it may be appropriate to temporarily separate the mother and newborn (or to have the newborn cared for by noninfected caregivers in the mother’s room) when the mother is acutely ill with COVID-19 and cannot care for the infant in a safe way. The AAP strongly supports breastfeeding as the best choice for feeding. Breast milk can be expressed after appropriate hygiene measures and fed by an uninfected caregiver. If the mother chooses to breastfeed the infant themselves, appropriate prevention measures are recommended. After discharge, advise mothers with COVID-19 to practice prevention measures (e.g., hand hygiene, respiratory hygiene/ mask) for newborn care until: they are afebrile for 24 hours without the use of antipyretics; at least 10 days have passed since symptoms first appeared (or 10 days since a positive test in asymptomatic women); and symptoms have improved. A newborn with documented infection but no symptoms requires close outpatient follow-up after discharge for 14 days after birth.[752]

### Management of people living with HIV

Recommendations for the triage, management, and treatment of COVID-19 in people with HIV are the same as those for the general population. Continue antiretroviral therapy and prophylaxis for opportunistic infections whenever possible, including patients who require hospitalization. Consult with a HIV specialist before adjusting or switching antiretroviral medications, and pay attention to potential drug-drug interactions and overlapping toxicities with COVID-19 treatments.[439]

### Treatment algorithm overview

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

#### mild COVID-19
- **1st** consider home isolation
- **plus** monitoring
- **plus** symptom management and supportive care
- **adjunct** antipyretic/analgesic
- **adjunct** experimental therapies

#### moderate COVID-19
- **1st** consider home isolation or hospital admission
- **plus** monitoring
- **plus** symptom management and supportive care
- **adjunct** antibiotics
- **adjunct** antipyretic/analgesic
- **adjunct** experimental therapies

#### severe COVID-19
- **1st** hospital admission
- **plus** consider oxygen therapy
- **plus** symptom management and supportive care
- **plus** venous thromboembolism prophylaxis
- **plus** monitoring
- **adjunct** antibiotics
- **adjunct** corticosteroid
- **adjunct** treatment of coinfections
- **adjunct** antipyretic/analgesic
- **adjunct** experimental therapies
- **adjunct** plan for discharge and rehabilitation
- **adjunct** palliative care

#### critical COVID-19
- **1st** intensive/critical care unit admission
- **plus** symptom management and supportive care
<table>
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<tr>
<th>Acute</th>
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<tbody>
<tr>
<td>plus</td>
<td>venous thromboembolism prophylaxis</td>
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<td>consider high-flow nasal oxygen or</td>
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<td>plus</td>
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<td>inhaled pulmonary vasodilator</td>
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<td>extracorporeal membrane oxygenation</td>
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<td>treatment of coinfections</td>
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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.
Coronavirus disease 2019 (COVID-19)

Management

Acute

<table>
<thead>
<tr>
<th>mild COVID-19</th>
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<tr>
<td>1st consider home isolation</td>
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- Patients with suspected or confirmed mild disease (i.e., symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia) and asymptomatic patients should be isolated to contain virus transmission.[136]

- Manage patients in a healthcare facility, in a community facility, or at home. Home isolation can be considered in most patients, with telemedicine or remote visits as appropriate.[136] [439] This decision requires careful clinical judgment and should be informed by an assessment of the patient’s home environment to ensure that: infection prevention and control measures and other requirements can be met (e.g., basic hygiene, adequate ventilation); the caregiver is able to provide care and recognize when the patient may be deteriorating; the caregiver has adequate support (e.g., food, supplies, psychological support); the support of a trained health worker is available in the community.[630] The location of care will depend on guidance from local health authorities and available resources.

- Pregnant women with suspected or confirmed mild disease may not require acute care in a hospital unless there is concern for rapid deterioration or an inability to return to hospital promptly.[136]

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


- Discontinue transmission-based precautions (including isolation) and release patients from the care pathway: 10 days after positive test (asymptomatic patients); 10 days after...
| Acute | symptom onset plus at least 3 days without fever and respiratory symptoms (symptomatic patients). The Centers for Disease Control and Prevention (CDC) recommends discontinuing home isolation once at least 10 days (or up to 20 days in patients who are severely immunocompromised) have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. In asymptomatic people, the CDC recommends discontinuing home isolation once at least 10 days have passed since the date of a positive test. For severely immunocompromised patients who are asymptomatic, isolation may be discontinued when at least 10 days and up to 20 days have passed since the date of a positive test; consider consultation with infectious diseases specialists and infection control experts. Alternatively, the CDC recommends at least two negative reverse-transcription polymerase chain reaction (RT-PCR tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients. If the patient is hospitalized, CDC guidance for discontinuing isolation is the same as for moderate disease (see below). Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 10 days in patients with milder disease who are managed in the community. |

plus monitoring

Treatment recommended for ALL patients in selected patient group

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

» 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.

plus symptom management and supportive care

Treatment recommended for ALL patients in selected patient group
Coronavirus disease 2019 (COVID-19)

Management

**Acute**

- Advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough.[478] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[671]

- Advise patients about adequate nutrition and appropriate rehydration. Advise patients to drink fluids regularly to avoid dehydration. Fluid intake needs can be higher than usual because of fever. However, too much fluid can worsen oxygenation.[136] [478]

- Advise patients to improve air circulation by opening a window or door.[478]

- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[136]

- Consider treatment for olfactory dysfunction (e.g., olfactory training) if it persists beyond 2 weeks. There is no evidence to support the use of these treatments in patients with COVID-19.[672]

**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.[136] [478] There is no evidence at present of severe adverse events in COVID-19 patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute
### Acute

Healthcare utilization, long-term survival, or quality of life in patients with COVID-19.\(^6\)\(^6\)\(^6\)\(^6\)\(^6\)\(^6\)\(^6\)\(^6\)\(^6\)

- 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 experimental therapies**

Treatment recommended for some patients in selected patient groups

- Consider appropriate experimental or emerging therapies.

- Antiviral therapies will have a greater effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies are likely to have a greater effect later in the course of the disease.\(^4\)\(^3\)\(^9\)

- See the Emerging section for more information.

### Moderate COVID-19

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

- Patients with suspected or confirmed moderate disease (i.e., clinical signs of pneumonia but no signs of severe pneumonia) should be isolated to contain virus transmission.\(^1\)\(^3\)\(^6\)\(^\)\(^\)

- Manage patients in a healthcare facility, in a community facility, or at home. Home isolation, with telemedicine or remote visits as appropriate, can be considered in low-risk patients. Manage patients at high risk of deterioration and pregnant women in a healthcare facility.\(^1\)\(^3\)\(^6\)\(^\)\(^\)\(^\)

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

» Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[136] The Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 10 days (not severely immunocompromised) or up to 20 days (severely immunocompromised) have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. In asymptomatic people, the CDC recommends discontinuing isolation once at least 10 days (not severely immunocompromised) or up to 20 days (severely immunocompromised) have passed since the date of a positive test. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative reverse-transcription polymerase chain reaction (RT-PCR) tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[673] If the patient is isolated at home, CDC guidance for discontinuing isolation is the same as for mild disease (see above). Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients, and 10 days in patients with milder disease who are managed in the community. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[663]
### Acute

» Closely monitor patients for signs or symptoms of disease progression. If the patient is being managed at home, counsel them about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain). Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalized. Patient education and appropriate follow-up are required. If the patient is being managed in hospital, monitor patients closely for signs of clinical deterioration using medical early warning scores (e.g., National Early Warning Score 2 [NEWS2]), and respond immediately with appropriate supportive care interventions.[136]

plus **symptom management and supportive care**

Treatment recommended for ALL patients in selected patient group

» Advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough.[478] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[671]

» Advise patients about adequate nutrition and appropriate rehydration. Advise patients to drink fluids regularly to avoid dehydration. Fluid intake needs can be higher than usual because of fever. However, too much fluid can worsen oxygenation.[136] [478]

» Advise patients to improve air circulation by opening a window or door.[478]

» Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[136]

» Consider treatment for olfactory dysfunction (e.g., olfactory training) if it persists beyond 2 weeks. There is no evidence to support the use of these treatments in patients with COVID-19.[672]

**adjunct antibiotics**

Treatment recommended for SOME patients in selected patient group
Consider empiric antibiotics only if there is clinical suspicion of secondary bacterial infection. Start treatment as soon as possible, and refer to local guidelines for choice of regimen. The regimen should be based on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.

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

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

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.

Acetaminophen or ibuprofen are recommended. There is no evidence at present of severe adverse events in COVID-19 patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilization, long-term survival, or quality of life in patients with COVID-19.

<table>
<thead>
<tr>
<th>Primary options</th>
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<tr>
<td><strong>Acetaminophen</strong>: 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</td>
</tr>
<tr>
<td><strong>Ibuprofen</strong>: 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</td>
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Coronavirus disease 2019 (COVID-19)

Management

Acute

» 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 experimental therapies

Treatment recommended for SOME patients in selected patient group

» Consider appropriate experimental or emerging therapies.

» Antiviral therapies will have a greater effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies are likely to have a greater effect later in the course of the disease.[439]

» See the Emerging section for more information.

severe COVID-19

1st hospital admission

» Patients with suspected or confirmed severe disease are at risk of rapid clinical deterioration and should be admitted to an appropriate healthcare facility under the guidance of a specialist team. Severe disease in adults is defined as having clinical signs of pneumonia plus at least one of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or \( \text{SpO}_2 <90\% \) on room air. Severe disease in children is defined as having clinical signs of pneumonia plus at least one of the following: central cyanosis or \( \text{SpO}_2 <90\% \), severe respiratory distress, general danger signs (inability to breastfeed or drink, lethargy or unconsciousness, or convulsions), or fast breathing (<2 months: ≥60 breaths per minute; 2-11 months: ≥50 breaths per minute; 1-5 years: ≥40 breaths per minute).[136]

» Use the Clinical Frailty Scale (CFS) to assess baseline health and inform discussions on treatment expectations when appropriate and within an individualised assessment of frailty. [Clinical Frailty Scale] (https://www.scfn.org.uk/clinical-frailty-scale) Do not use the CFS for younger people, people with stable long-term disabilities (e.g., cerebral palsy), learning disabilities, or autism. Make an individualized assessment of frailty in these people, using clinical assessment and alternative scoring methods.[478] A meta-analysis found that an increase in CFS was associated with an
Coronavirus disease 2019 (COVID-19) Management

Acute increase in mortality (each 1-point increase in CFS was associated with a 12% increase in mortality). However, some studies suggest that a more nuanced understanding of frailty and outcomes is needed, and you should exercise caution in placing too much emphasis on the influence of frailty alone when discussing prognosis in older people.

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

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

» Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms. The Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 10 days and up to 20 days have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. Consider consultation with infection control experts before discontinuing isolation. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative reverse-transcription polymerase chain reaction (RT-PCR) tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.

Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients.
patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[663]

plus **consider oxygen therapy**

Treatment recommended for ALL patients in selected patient group

» Start supplemental oxygen therapy immediately in any patient with emergency signs (i.e., obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions), or any patient without emergency signs and \( \text{SpO}_2 < 90\% \).[136] [439]

» Target \( \text{SpO}_2 \) to \( \geq 94\% \) during resuscitation in adults and children with emergency signs who require emergency airway management and oxygen therapy. Once the patient is stable, a target \( \text{SpO}_2 > 90\% \) in children and nonpregnant adults, and \( \geq 92\% \) to 95% in pregnant women, is recommended. Nasal prongs or a nasal cannula are preferred in young children.[136] Some guidelines recommend that \( \text{SpO}_2 \) should be maintained no higher than 96%.[678]

» Some centers may recommend different \( \text{SpO}_2 \) targets in order to support prioritization of oxygen flow for the most severely ill patients in hospital. NHS England recommends a target of 92% to 96% (or 90% to 94% if clinically appropriate), for example.[679]

» Consider positioning techniques (e.g., high supported sitting), and airway clearance management to optimize oxygenation and assist with secretion clearance in adults. Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require supplemental oxygen.[136] [439] Early self-proning of awake, nonintubated patients has been shown to improve oxygen saturation and may delay or reduce the need for intensive care.[680] [681] [682] [683] [684]

» Monitor patients closely for signs of progressive acute hypoxemic respiratory failure.[136] [439]

plus **symptom management and supportive care**

Treatment recommended for ALL patients in selected patient group
Acute

» Fluids and electrolytes: use cautious fluid management in adults and children without tissue hypoperfusion and fluid responsiveness as aggressive fluid resuscitation may worsen oxygenation.[136] Correct any electrolyte or metabolic abnormalities, such as hyperglycemia or metabolic acidosis, according to local protocols.[685]

» Cough: advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough. Short-term use of a cough suppressant may be considered in select patients (e.g., if the cough is distressing to the patient) provided there are no contraindications.[478] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[671]

» Breathlessness: keep the room cool, and encourage relaxation, breathing techniques, and changing body positions. Identify and treat any reversible causes of breathlessness (e.g., pulmonary edema, pulmonary embolism, COPD, asthma). Consider a trial of oxygen, if available.[478]

» Anxiety, delirium, and agitation: identify and treat any underlying or reversible causes (e.g., offer reassurance, treat hypoxia, correct metabolic or endocrine abnormalities, address coinfections, minimize use of drugs that may cause or worsen delirium, treat substance withdrawal, maintain normal sleep cycles, treat pain or breathlessness).[136] [478] Low doses of haloperidol (or another suitable antipsychotic) can be considered for agitation.[136] Nonpharmacologic interventions are the mainstay for the management of delirium when possible, and prevention is key.[686]

» 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.[687]

» Mental health symptoms: provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia or depression as appropriate.[136]

plus venous thromboembolism prophylaxis

Treatment recommended for ALL patients in selected patient group
## Acute Management

### Primary options

- **enoxaparin**: consult specialist for guidance on dose

  OR

- **dalteparin**: consult specialist for guidance on dose

### Secondary options

- **fondaparinux**: consult specialist for guidance on dose

  OR

- **heparin**: consult specialist for guidance on dose

  » Assess the risk of bleeding as soon as possible after admission, or by the time of the first consultant review, using a suitable risk assessment tool.[478]

  » Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalized adults and adolescents, provided there are no contraindications.[136] [439] [688] [689] The UK National Institute for Health and Care Excellence (NICE) recommends starting as soon as possible and within 14 hours of admission, and continuing for a minimum of 14 days or until discharge.[478] For hospitalized children, indications for VTE prophylaxis should be the same as those for children without COVID-19.[439]

  » Low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options for standard thromboprophylaxis.[136] NICE recommends low molecular weight heparin first-line, with fondaparinux or unfractionated heparin reserved for patients who cannot have low molecular weight heparin.[478] Unfractionated heparin is contraindicated in patients with severe thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia. Mechanical thromboprophylaxis (e.g., intermittent pneumatic compression devices) is recommended if anticoagulation is contraindicated or not available.[689] [691]

  » The optimal dose is yet to be determined. Standard prophylaxis doses are generally recommended over intermediate- or full
management of COVID-19 patients without an established indication for higher-dose anticoagulation. However, this recommendation varies and you should consult your local guidelines. The World Health Organization recommends standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing in patients without an established indication for higher-dose anticoagulation.[136] NICE recommends clinicians consider a treatment dose of a low molecular weight heparin in young people and adults who are likely to be in hospital for at least 3 days and need supplemental oxygen (but who are not yet receiving high-flow oxygen, continuous positive airway pressure, noninvasive ventilation, or invasive mechanical ventilation), unless contraindicated. This is because of fewer deaths and less likelihood of needing intensive care with this dose compared with a standard prophylaxis dose without a notable increase in major bleeding, although the evidence for this recommendation is weak. Treatment should be for a minimum of 14 days or until discharge, and the dose may need to be reduced if the clinical circumstances change (such as a need for advanced respiratory support). For those who do not need supplemental oxygen, follow standard VTE prophylaxis guidelines.[478] The National Institutes of Health guidelines panel recommends prophylactic-dose anticoagulation, and states that there are insufficient data to recommend increased anticoagulant doses for VTE prophylaxis in COVID-19 patients outside the setting of a clinical trial.[439]

» Dose adjustments may be required in patients with extremes of body weight or renal impairment.[478]

» For patients who are already on an anticoagulant for another condition, continue the patient’s current therapeutic dose unless contraindicated by a change in clinical circumstances. Consider switching to low molecular weight heparin as the preferred option for venous thromboembolism prophylaxis if the patient’s clinical condition is deteriorating and the patient is not currently on low molecular weight heparin.[478]

» Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected.[136] If the patient’s clinical condition changes, assess the
Acute risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.\[478\]

» Continue until hospital discharge.\[136\] Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients.\[439\] \[688\] \[689\] Ensure patients who require VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.\[478\]

» There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulation in hospitalized patients with COVID-19.\[692\] A retrospective analysis of over 4000 patients found that anticoagulation was associated with lower mortality and intubation among hospitalized COVID-19 patients. Therapeutic anticoagulation was associated with lower mortality compared with prophylactic anticoagulation, but the difference was not statistically significant.\[693\] An observational cohort study of over 4000 patients found that early initiation of prophylactic anticoagulation in hospitalized patients was associated with a decreased risk of 30-day mortality and no increased risk of serious bleeding events compared with no anticoagulation.\[694\] Clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.\[688\]

plus monitoring

Treatment recommended for ALL patients in selected patient group

» Monitor patients closely for signs of clinical deterioration, and respond immediately with appropriate supportive care interventions.\[136\]

adjunct antibiotics

Treatment recommended for SOME patients in selected patient group

» Consider empiric antibiotics if there is clinical suspicion of secondary bacterial infection. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria (or within 4 hours of establishing a diagnosis of secondary bacterial pneumonia); do not wait for microbiology results. Base the regimen on the clinical diagnosis (e.g., community-acquired pneumonia, hospital-acquired pneumonia, sepsis), local epidemiology and susceptibility data, and local treatment guidelines.\[136\] \[439\] \[478\]
**Acute**

- 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.[478] There is insufficient evidence to recommend empiric broad-spectrum antibiotics in the absence of another indication.[439]

- Consider seeking specialist advice for people who: are immunocompromised; have a history of infection with resistant organisms; have a history of repeated infective exacerbations of lung disease; are pregnant; or are receiving advanced respiratory or organ support. Seek specialist advice if there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic, or there is clinical or microbiologic evidence of infection and the person’s condition does not improve as expected after 48 to 72 hours of antibiotic treatment.[478]

- Reassess antibiotic use daily. De-escalate empiric therapy on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching from intravenous to oral therapy. Duration of treatment should be as short as possible (e.g., 5 to 7 days). Antibiotic stewardship programs should be in place.[136]

<table>
<thead>
<tr>
<th>adjunct</th>
<th>corticosteroid</th>
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<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
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</table>

**Primary options**

- **dexamethasone**: adults: 6 mg orally/intravenously once daily for 7-10 days

  OR

- **hydrocortisone**: adults: 50 mg orally/intravenously every 8 hours for 7-10 days

**Secondary options**

- **prednisone**: adults: 40 mg/day orally given in 1-2 divided doses for 7-10 days

  OR

- **methylprednisolone**: adults: 32 mg/day orally/intravenously given in 1-2 divided doses for 7-10 days

- 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
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with severe COVID-19. This recommendation is based on two meta-analyses that pooled data from eight randomized trials (over 7000 patients), including the UK RECOVERY trial. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe and critical COVID-19. They also probably reduce the need for invasive ventilation. There is no evidence directly comparing dexamethasone and hydrocortisone. The harms of treatment in this context are considered to be minor. It is unclear whether these recommendations can be applied to children or those who are immunocompromised. There is also evidence that corticosteroids probably reduce the length of intensive care unit stay (low certainty), and increase ventilator-free days (moderate certainty).

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

» In Europe, the European Medicines Agency has endorsed the use of dexamethasone for patients with severe disease who require oxygen therapy or mechanical ventilation.

» In the US, the National Institutes of Health guidelines panel recommends dexamethasone, either alone or in combination with remdesivir (see the Emerging section for information on remdesivir), in hospitalized patients who require supplemental oxygen. The panel recommends against using dexamethasone in patients who do not require supplemental oxygen. Alternative corticosteroids may be used in situations where dexamethasone is not available. The Infectious Diseases Society of America supports the use of dexamethasone in hospitalized patients with severe disease.

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

adjunct treatment of coinfections

Treatment recommended for SOME patients in selected patient group

» Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols. The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection. Start empiric treatment with oseltamivir in hospitalized
patients who are suspected of having either or both infections as soon as possible without waiting for influenza test results. Antiviral therapy can be stopped once influenza has been ruled out.[439]

**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.[136] [478] There is no evidence at present of severe adverse events in COVID-19 patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilization, long-term survival, or quality of life in patients with COVID-19.[664] [665] [666] [667] [668] [669] [670]

» 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 experimental therapies**

Treatment recommended for SOME patients in selected patient group

- Consider appropriate experimental or emerging therapies.

- Antiviral therapies will have a greater effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies are likely to have a greater effect later in the course of the disease.[439]
Management

**Acute**

- See the Emerging section for more information.

**adjunct plan for discharge and rehabilitation**

Treatment recommended for SOME patients in selected patient group

- Routinely assess older patients for mobility, functional swallow, cognitive impairment, and mental health concerns, and based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[136]

**adjunct palliative care**

Treatment recommended for SOME patients in selected patient group

- Palliative care interventions should be made accessible at each institution that provides care for patients with COVID-19. Identify whether the patient has an advance care plan and respect the patient’s priorities and preferences when formulating the patient’s care plan.[136] Follow local palliative care guidelines.

**critical COVID-19**

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

- 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 under the guidance of a specialist team.[136]

- Discuss the risks, benefits, and potential outcomes of treatment options with patients and their families, and allow them to express preferences about their management. Take their wishes and expectations into account when considering the ceiling of treatment. Use decision support tools if available. Put treatment escalation plans in place, and discuss any existing advance care plans or advance decisions to refuse treatment with patients who have preexisting advanced comorbidities.[478]

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

- Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as midwifery and mental health and psychosocial support. A woman-centered, respectful, skilled approach to care is
Acute

Management

Coronavirus disease 2019 (COVID-19)

Management

» Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[136] The Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 10 days and up to 20 days have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. Consider consultation with infection control experts before discontinuing isolation. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative reverse-transcription polymerase chain reaction (RT-PCR) tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[673] Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[663]

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 above for more detailed information.

» Follow local guidelines for the management of pain, sedation, and delirium.[439]
### Acute

» Implement standard interventions to prevent complications associated with critical illness.[136]

**plus** **venous thromboembolism prophylaxis**

Treatment recommended for ALL patients in selected patient group

**Primary options**

» *enoxaparin*: consult specialist for guidance on dose

OR

» *dalteparin*: consult specialist for guidance on dose

**Secondary options**

» *heparin*: consult specialist for guidance on dose

OR

» *fondaparinux*: consult specialist for guidance on dose

» Unfractionated heparin is preferred over fondaparinux in critically ill patients if low molecular weight heparin, as the preferred option for venous thromboembolism prophylaxis, cannot be used.[689]

» The UK National Institute for Health and Care Excellence (NICE) does not recommend treatment-dose low molecular weight heparin for VTE prophylaxis for patients receiving advanced respiratory support unless the patient is part of a nationally approved clinical trial because it is likely to cause harm in this group. NICE recommends reducing the dose to a locally agreed intermediate or standard dose and reassessing VTE and bleeding risks daily in patients who progress to needing high-flow oxygen, continuous positive airway pressure, noninvasive or invasive mechanical ventilation, or palliative care.[478]

» NHS England recommends that therapeutic doses should not be offered unless there is a standard indication for therapeutic anticoagulation, as trials show that therapeutic doses do not improve clinical outcome of severe disease in the critical care setting.[739]
» Some guidelines recommend that escalated doses can be considered in critically ill patients.[688] [740]

» A multicenter randomized controlled trial found that intermediate-dose prophylactic anticoagulation did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or 30-day mortality compared with standard-dose prophylactic anticoagulation among patients admitted to the intensive care unit. These results do not support the routine empiric use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the intensive care unit.[741]

» Dose adjustments may be required in patients with extremes of body weight or renal impairment.[478]

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

plus consider high-flow nasal oxygen or noninvasive ventilation

Treatment recommended for ALL patients in selected patient group

» Consider a trial of high-flow nasal oxygen (HFNO) or noninvasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in selected patients with mild acute respiratory distress syndrome. Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require HFNO or noninvasive ventilation.[136]

» Airborne precautions are recommended for these interventions (including bubble CPAP) due to uncertainty about the potential for aerosolization.[136]

» Patients with hypercapnia, hemodynamic instability, multi-organ failure, or abnormal mental status should generally not receive HFNO, although emerging data suggest that it may be safe in patients with mild to moderate and nonworsening hypercapnia. Patients with hypoxemic respiratory failure and hemodynamic instability, multi-organ failure, or abnormal mental status should not receive these treatments in place of other options such as invasive ventilation.[136]
Acute

» There is ongoing debate about the optimal mode of respiratory support before mechanical ventilation.[708] NHS England recommends CPAP as the preferred form of noninvasive ventilation in patients with hypoxemic (type 1) respiratory failure. It doesn't advocate the use of HFNO based on a lack of efficacy, oxygen use (HFNO can place a strain on oxygen supplies with the risk of site supply failure), and infection spread.[709] Other guidelines recommend HFNO over noninvasive ventilation, unless HFNO is not available.[439] [678] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[710]

» Early CPAP may provide a bridge to invasive mechanical ventilation. Reserve the use of BiPAP for patients with hypercapnic acute on chronic ventilatory failure (type 2 respiratory failure).[709]

» Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions, they require urgent endotracheal intubation.[136] [678]

plus consider invasive mechanical ventilation

Treatment recommended for ALL patients in selected patient group

» Consider endotracheal intubation and mechanical ventilation in patients who are acutely deteriorating despite advanced oxygen/noninvasive ventilatory support measures.[136] [439]

» Endotracheal intubation should be performed by an experienced provider using airborne precautions.[136] Intubation by video laryngoscopy is recommended if possible.[439] Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require preoxygenation with 100% fraction of inspired oxygen (FiO₂) for 5 minutes.[136]

» Mechanically ventilated patients with acute respiratory distress syndrome (ARDS) should receive a lung-protective, low tidal volume/low inspiratory pressure ventilation strategy (lower targets are recommended in children). A higher positive end-expiratory pressure (PEEP) strategy is preferred over a lower PEEP strategy in moderate to severe ARDS. However, individualization of PEEP, where the patient is monitored for beneficial or harmful effects and driving pressure during titration
with consideration of the risks and benefits of PEEP titration, is recommended.\[136\] \[439\] \[678\] NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.\[718\]

» Although some patients with COVID-19 pneumonia meet the criteria for ARDS, there is some discussion about whether COVID-19 pneumonia is its own specific disease with atypical phenotypes. Anecdotal evidence suggests that the main characteristic of the atypical presentation is the dissociation between well-preserved lung mechanics and the severity of hypoxemia.\[719\] \[720\] \[721\] \[722\] \[723\] \[724\] However, this approach has been criticized.\[725\] \[726\] 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.\[727\] As a consequence of this, some clinicians have warned that protocol-driven ventilator use may be causing lung injury in some patients, and that ventilator settings should be based on physiologic findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.\[719\] PEEP should always be carefully titrated.\[728\]

» 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.\[136\] \[439\] \[678\] Longer durations may be feasible in some patients.\[729\]

» Lung recruitment maneuvers are suggested, but staircase recruitment maneuvers are not recommended.\[439\] \[678\]

**adjunct**  **inhaled pulmonary vasodilator**

Treatment recommended for SOME patients in selected patient group

» Consider a trial of an inhaled pulmonary vasodilator in adults who have severe acute respiratory distress syndrome and hypoxemia despite optimizing ventilation. Taper off if there is no rapid improvement in oxygenation.\[439\] \[678\]

**adjunct**  **extracorporeal membrane oxygenation**

Treatment recommended for SOME patients in selected patient group

» Consider extracorporeal membrane oxygenation (ECMO) according to availability
### Acute

and expertise if the above methods fail. [136] [678] [733] [734] ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO. [735]

» There is insufficient evidence to recommend either for or against the routine use of ECMO. [439]

» The estimated 60-day survival rate of ECMO-rescued patients with COVID-19 (31%) was similar to that of previous studies of ECMO for severe ARDS. [736]

» An international cohort study of 1035 patients found that both the estimated mortality 90 days after ECMO initiation and mortality in those who achieved a final outcome of death or discharge were <40%, consistent with previously reported survival rates in acute hypoxic respiratory failure. [737]

» Single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure. [738]

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**Primary options**

» **dexamethasone**: adults: 6 mg orally/intravenously once daily for 7-10 days

OR

» **hydrocortisone**: adults: 50 mg orally/intravenously every 8 hours for 7-10 days

**Secondary options**

» **prednisone**: adults: 40 mg/day orally given in 1-2 divided doses for 7-10 days

OR
### Acute

- **methylprednisolone**: adults: 32 mg/day orally/intravenously given in 1-2 divided doses for 7-10 days

- 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 COVID-19. This recommendation is based on two meta-analyses that pooled data from eight randomized trials (over 7000 patients), including the UK RECOVERY trial. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe and critical COVID-19. They also probably reduce the need for invasive ventilation. There is no evidence directly comparing dexamethasone and hydrocortisone. The harms of treatment in this context are considered to be minor. It is unclear whether these recommendations can be applied to children or those who are immunocompromised.[652] [696] [697] [698] There is also evidence that corticosteroids probably reduce the length of intensive care unit stay (low certainty), and increase ventilator-free days (moderate certainty).[699] [760]

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

- In Europe, the European Medicines Agency has endorsed the use of dexamethasone for patients with severe disease who require oxygen therapy or mechanical ventilation.[701]

- In the US, the National Institutes of Health guidelines panel recommends using dexamethasone, either alone or in combination with remdesivir (see the Emerging section for information on remdesivir), in hospitalized patients who require high-flow oxygen or noninvasive ventilation. The panel recommends dexamethasone alone in patients on mechanical ventilation or extracorporeal membrane oxygenation. Alternative corticosteroids may be used in situations where dexamethasone is not available.[439] The Infectious Diseases Society of America supports the use of dexamethasone in hospitalized patients with severe disease.[702]

  - Monitor patients for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.[439]
A meta-analysis found an increased risk of venous thromboembolism with corticosteroid administration in patients with critical disease. However, no definite findings were available due to the differing corticosteroid regimens and the heterogeneity of the studies.[742]

adjunct treatment of coinfections

Treatment recommended for SOME patients in selected patient group

» Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.[136] The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection. Start empiric treatment with oseltamivir in hospitalized patients who are suspected of having either or both infections as soon as possible without waiting for influenza test results. Antiviral therapy can be stopped once influenza has been ruled out.[439]

adjunct experimental therapies

Treatment recommended for SOME patients in selected patient group

» Consider appropriate experimental or emerging therapies.

» Antiviral therapies will have a greater effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies are likely to have a greater effect later in the course of the disease.[439]

» See the Emerging section for more information.

adjunct plan for discharge and rehabilitation

Treatment recommended for SOME patients in selected patient group

» Routinely assess intensive care patients for mobility, functional swallow, cognitive impairment, and mental health concerns, and based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[136]

adjunct palliative care

Treatment recommended for SOME patients in selected patient group

» Palliative care interventions should be made accessible at each institution that provides care for patients with COVID-19. Identify whether the patient has an advance care plan and respect
### Acute

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<th>the patient’s priorities and preferences when formulating the patient’s care plan.[136] Follow local palliative care guidelines.</th>
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Emerging

Interleukin-6 (IL-6) inhibitors

IL-6 inhibitors inhibit IL-6-mediated signaling by competitively binding to IL-6 receptors. IL-6 is a proinflammatory cytokine. These drugs (e.g., tocilizumab, siltuximab) are being trialed in patients for the treatment of SARS-CoV-2-induced cytokine release syndrome. They are already approved in some countries for certain conditions, but are off-label for this indication. UK guidance recommends considering a single dose of tocilizumab in hospitalized adults who meet the following criteria: infection is confirmed by microbiologic testing or where a multidisciplinary team has a high level of confidence that the clinical and radiologic features suggest that COVID-19 is the most likely diagnosis; AND the patient is receiving (or has completed a course of) dexamethasone or an equivalent corticosteroid (unless contraindicated); AND C-reactive protein level is ≥75 mg/L; AND oxygen saturation is <92% on room air OR there is a requirement for supplemental oxygen; OR an IL-6 inhibitor has not already been administered during the admission and within 24 to 48 hours of commencement of respiratory support.[761] UK guidance continues to only recommend a single dose of sarilumab in critically ill adults with pneumonia requiring respiratory support (high-flow nasal oxygen, continuous positive airway pressure or noninvasive ventilation, or invasive mechanical ventilation) when infection is confirmed by microbiologic testing (or where a multidisciplinary team has a high level of confidence that the clinical and radiologic features suggest that COVID-19 is the most likely diagnosis). Patients must meet specific eligibility criteria (and not meet exclusion criteria). These recommendations are based on data from the UK RECOVERY and REMAP-CAP trials. Preliminary data (yet to be peer reviewed) from the UK RECOVERY trial found that tocilizumab reduced 28-day mortality compared with usual care in patients who required oxygen and had evidence of inflammation. The results showed that 29% of patients in the tocilizumab group died within 28 days compared with 33% in the usual care group, a 14% reduction in relative mortality. Tocilizumab also increased the probability of discharge alive within 28 days from 47% to 54%. These benefits were seen regardless of the level of respiratory support, and were additional to the benefits of corticosteroids.[762] Data from the REMAP-CAP trial showed more organ support-free days and a reduction in mortality when IL-6 inhibitors were given to critically ill patients receiving organ support in the intensive care unit within 24 hours of admission, compared with standard of care (including corticosteroids in the majority of patients).[763] According to the UK National Institute for Health and Care Excellence, it is possible that any benefit from tocilizumab or sarilumab is more likely with earlier use, when disease progression and any developing organ dysfunction may be more reversible.[764] [765] The US National Institutes of Health guidelines panel recommends a single dose of tocilizumab, in combination with dexamethasone (or a suitable alternative corticosteroid), in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to progressive COVID-19. This includes: recently hospitalized patients (e.g., within 3 days) who have been admitted to the intensive care unit within the prior 24 hours and who require invasive mechanical ventilation, noninvasive mechanical ventilation, or high-flow nasal oxygen; OR recently hospitalized patients, not in the intensive care unit, with rapidly increasing oxygen needs who require noninvasive mechanical ventilation or high-flow nasal oxygen and have significantly increased markers of inflammation (e.g., C-reactive protein level is ≥75 mg/L). Some panel members also recommend tocilizumab in patients who are exhibiting rapidly increasing oxygen needs while on a corticosteroid and have a C-reactive protein level ≥75 mg/L but who do not yet require noninvasive mechanical ventilation or high-flow nasal oxygen. However, there is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Tocilizumab should be given only in combination with a corticosteroid.[439] The Infectious Diseases Society of America recommends tocilizumab in hospitalized adults with progressive severe or critical disease who have elevated markers of systemic inflammation, in addition to standard of care (i.e., corticosteroids), rather than standard of care alone.[702] This recommendation is conditional, based on low-certainty evidence. Patients, particularly those who respond to corticosteroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab. There are conflicting recommendations across international guidelines about the use of these agents, so it is important that you check local guidance and protocols. Evidence is emerging. A Cochrane living systematic review found that tocilizumab reduced all-cause mortality at day 28, and probably resulted in slightly fewer serious adverse events compared with standard care alone or placebo. The evidence suggests uncertainty around the effect on mortality after day 60. However, tocilizumab probably results in little or no increase in clinical improvement at day 28 (i.e., hospital discharge or improvement measured by trialist-defined scales). The impact of tocilizumab on other outcomes is uncertain. More data are needed to be able to identify which patients are more likely to benefit from this treatment. Evidence for an effect of
**Remdesivir**

Remdesivir is an investigational broad-spectrum antiviral agent that inhibits RNA-dependent RNA polymerase. It is approved in many countries for the treatment of COVID-19. In the UK and Europe, remdesivir has been conditionally approved in adolescents (≥12 years of age who weigh at least 40 kg) and adults with pneumonia who require supplemental oxygen (low- or high-flow oxygen or other noninvasive ventilation at start of treatment).[779] In the US, remdesivir has been approved for the treatment of adolescents (≥12 years of age who weigh at least 40 kg) and adults who require hospitalization, and has emergency-use authorization for use in children.[780] The World Health Organization recommends against the use of remdesivir in hospitalized patients in addition to standard care, regardless of disease severity.[852] [697] This weak or conditional recommendation is based on a systematic review and network meta-analysis of four randomized trials with 7333 hospitalized patients, and included the NIAID-ACTT-1 trial (on which the original US approval of remdesivir was based) and the WHO Solidarity trial. There is currently no evidence that remdesivir improves patient outcomes such as time to clinical improvement, the need for mechanical ventilation, or mortality. However, the meta-analysis did not prove that remdesivir has no benefit.[697] The WHO Solidarity trial found that remdesivir appears to have little or no effect on hospitalized patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[781] Another living systematic review and network meta-analysis found that remdesivir may not reduce mortality (low-certainty evidence) or time to symptom resolution (moderate-certainty evidence) compared with standard care.[699] [760] The UK National Institute for Health and Care Excellence recommends remdesivir in adults and children ≥12 years of age and ≥40 kg who are in hospital and on supplemental oxygen but not on invasive mechanical ventilation.[478] Complete the 5-day course of treatment if remdesivir has been started and there is subsequent progression to invasive mechanical ventilation. The US National Institutes of Health guidelines panel recommends remdesivir in hospitalized patients who require supplemental oxygen.[439] It may be given alone (e.g., for patients who require minimal supplemental oxygen) or in combination with dexamethasone (e.g., for patients who require increasing amounts of supplemental oxygen). The panel also recommends remdesivir, in combination with dexamethasone, in hospitalized patients who require high-flow oxygen or noninvasive ventilation. It does not recommend remdesivir in patients who require invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). The panel acknowledges that remdesivir may also be appropriate in hospitalized patients who do not require oxygen, but who are at high risk of disease progression. The recommended treatment course is 5 days or until hospital discharge, whichever comes first. Some experts recommend a 10-day course in patients who have not shown substantial clinical improvement by day 5. The Infectious Diseases Society of America recommends remdesivir in hospitalized patients with severe disease.[702] This recommendation is based on moderate-certainty evidence. The recommended treatment course is 5 days in patients on oxygen, and 10 days in patients on mechanical ventilation or ECMO. The panel recommends against the routine use of remdesivir in hospitalized patients who do not require oxygen and have an oxygen saturation >94% on room air, based on very low-certainty evidence. There are conflicting recommendations across international guidelines about the use of remdesivir, so it is important that you check local guidance and protocols. Consult local drug formulary...
for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Casirivimab/imdevimab

Casirivimab and imdevimab are intravenous investigational neutralizing human immunoglobulin G-1 monoclonal antibodies with activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The two antibodies bind to nonoverlapping epitopes of the receptor-binding domain of the spike protein to block virus entry into host cells. Casirivimab/imdevimab (formerly known as REGN-COV2) has been granted an emergency-use authorization in the US for the treatment of mild to moderate disease in children and adults.[782] The US emergency-use authorization covers patients with positive results of direct viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe disease and/or hospitalization. This includes patients who are 65 years of age or older, or who have certain chronic medical conditions. The European Medicines Agency has issued advice that casirivimab/imdevimab may be used in patients ages 12 years and older who do not require supplemental oxygen and who are at high risk of progressing to severe disease; however, the agency is yet to issue a marketing authorization.[783] The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for or against the use of casirivimab/imdevimab for the treatment of outpatients with mild to moderate COVID-19, and that it should not be considered the standard of care.[439] Patients at higher risk for disease progression should be prioritized for treatment, and patients who are hospitalized should not receive casirivimab/imdevimab outside of a clinical trial. The Infectious Diseases Society of America suggests against the routine use of casirivimab/imdevimab in ambulatory patients.[702] However, it recommends that casirivimab/imdevimab may be a reasonable treatment option in ambulatory patients or patients with mild to moderate disease who are admitted to the hospital for the management of conditions other than COVID-19 and who are at increased risk of progressing to severe disease, after informed decision-making. Evidence is emerging. Emergency-use authorization was based on a randomized, double-blind, placebo-controlled trial in nonhospitalized adults with mild to moderate symptoms that found that casirivimab/imdevimab reduced hospitalization or emergency department visits in patients at high risk for disease progression within 28 days after treatment, when compared with placebo. This study is yet to be published.[782] An interim analysis of an ongoing, randomized, double-blind, phase 1-3 trial in nonhospitalized patients found that casirivimab/imdevimab reduced viral load from baseline through to day 7, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline.[784] Casirivimab/imdevimab is not authorized for use in hospitalized patients or those who require oxygen as it has not shown benefit in these patients. Further enrollment of patients requiring high-flow oxygen or mechanical ventilation has been placed on hold due to a potential safety signal and an unfavorable risk/benefit profile at this time. However, enrollment of hospitalized patients requiring either no or low-flow oxygen is being continued.[785] According to a press release from the manufacturer, results from a phase 3 trial found that casirivimab/imdevimab reduced the risk of hospitalization or death by 70% in nonhospitalized patients.[786] Results are yet to be published. According to another press release from the manufacturer, interim results from an ongoing phase 3 trial evaluating casirivimab/imdevimab for prevention in people at high risk of infection due to household exposure found that passive vaccination with casirivimab/imdevimab resulted in prevention of symptomatic infection in 100% of patients compared with placebo (8 cases in the placebo group compared with 0 in the casirivimab/imdevimab group), and 50% lower overall rates of symptomatic or asymptomatic infection.[787] Results are yet to be published. Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug. Circulating SARS-CoV-2 variants may be associated with resistance to monoclonal antibodies. Consult local guidance for details regarding specific variants and resistance.

Bamlanivimab/etesevimab

Bamlanivimab (formerly known as LY-CoV555) and etesevimab (formerly known as LY-CoV016) are intravenous investigational neutralizing human immunoglobulin G-1 monoclonal antibodies with activity against SARS-CoV-2. The two antibodies bind to different, but overlapping, epitopes of the receptor-binding domain of the spike protein to block virus entry into host cells. Bamlanivimab monotherapy and bamlanivimab/etesevimab have been granted an emergency-use authorization in the US for the treatment of mild to moderate disease in children and adults.[788] [789] The US emergency-use authorizations cover patients with positive results of direct viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe disease and/or hospitalization. This includes patients who are 65 years of age or older, or who have certain chronic medical conditions. The
European Medicines Agency has issued advice that bamlanivimab/etesevimab may be used in patients ages 12 years and older who do not require supplemental oxygen and who are at high risk of progressing to severe disease. The agency is yet to issue a marketing authorization, but has started a rolling review of the data. The agency also concluded that despite uncertainties around the benefits of bamlanivimab/etesevimab, it can be considered a treatment option for this indication.[790] The US National Institutes of Health guidelines panel recommends bamlanivimab/etesevimab for the treatment of outpatients with mild to moderate disease who are at high risk of clinical progression (as defined by the emergency-use authorization criteria).[439] Treatment should be started as soon as possible after the patient has received a positive test result and within 10 days of symptom onset. The panel recommends against the use of bamlanivimab/etesevimab in patients who are hospitalized, except in the context of a clinical trial. However, the combination should be considered in patients with mild to moderate disease who are hospitalized for a reason other than COVID-19 but who otherwise meet the emergency-use authorization criteria. The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for or against the use of bamlanivimab monotherapy for the treatment of outpatients with mild to moderate disease, and that it should not be considered the standard of care.[439] Patients at higher risk for disease progression should be prioritized for treatment, and patients who are hospitalized should not receive bamlanivimab outside of a clinical trial. The Infectious Diseases Society of America recommends bamlanivimab/etesevimab in ambulatory patients with mild to moderate disease who are at high risk for progression to severe disease, based on low-certainty evidence. The panel recommends against the use of bamlanivimab monotherapy in hospitalized patients with severe disease.[702] Patients with mild to moderate disease who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive bamlanivimab/etesevimab. Evidence is emerging. A trial investigating the efficacy of bamlanivimab in hospitalized patients has been stopped based on trial data that suggest bamlanivimab is unlikely to help hospitalized patients recover from advanced disease. Other studies of bamlanivimab in recently diagnosed mild to moderate disease, recently diagnosed disease in the ambulatory setting, and prevention of disease in residents and staff at long-term care facilities remain ongoing.[791] Bamlanivimab, in combination with remdesivir, did not demonstrate efficacy among hospitalized patients who had COVID-19 without organ failure.[792] Among patients with mild to moderate disease, treatment with bamlanivimab/etesevimab was associated with a significant reduction in viral load at day 11 compared with placebo; however, no significant difference in viral load reduction was observed with bamlanivimab monotherapy.[793] According to press releases from the manufacturer, bamlanivimab/etesevimab reduced the risk of infection by 80% in a nursing home in the BLAZE-2 trial, and bamlanivimab/etesevimab reduced the risk of hospitalizations and death in high-risk patients by 87% in the BLAZE-1 trial; however, results are yet to be published.[794] [795] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug. Circulating SARS-CoV-2 variants may be associated with resistance to monoclonal antibodies. Consult local guidance for details regarding specific variants and resistance.

**Convalescent plasma**

Convalescent plasma is a blood product that contains antibodies to SARS-CoV-2 from patients who have recovered. High-titer convalescent plasma (i.e., plasma with high SARS-CoV-2 antibody titers) has been granted an emergency-use authorization in the US for the treatment of hospitalized patients early in the disease course, and to those hospitalized patients who have impaired humoral immunity and cannot produce an adequate antibody response. Low-titer convalescent plasma is no longer authorized.[796] It has not been authorized for this indication in the UK or Europe. UK guidance recommends that convalescent plasma should not be used in the management of hospitalized patients with suspected or confirmed infection.[797] This recommendation is based on data from the UK RECOVERY and REMAP-CAP trials. Preliminary data (yet to be peer reviewed) from the UK RECOVERY trial found that high-titer convalescent plasma did not improve survival or other prespecified clinical outcomes among hospitalized patients.[798] Early data from the REMAP-CAP study found that treatment with convalescent plasma did not improve outcomes among patients requiring intensive care unit support, according to a press release.[799] Results are yet to be published. The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of convalescent plasma.[439] The Infectious Diseases Society of America recommends convalescent plasma only in the context of a clinical trial.[702] Evidence is emerging. Emergency-use authorization was based on the preprint (not peer reviewed) publication of an open-label, multicenter, expanded access program study of over 35,000 patients that found convalescent plasma lowered 7-day mortality by 9% in hospitalized patients when given within 3 days of diagnosis, and by 12% when given 4 or more days later.[800] A meta-analysis and systematic review of four peer-reviewed randomized controlled trials (1060 patients) and six unpublished randomized controlled trials (10,722
patients) 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, based on low- to moderate-certainty evidence.[801] A randomized, double-blind, placebo-controlled trial in older patients with mild disease who received convalescent plasma within 72 hours after the onset of symptoms found that early administration reduced the progression to severe disease.[802] A Cochrane review found that currently available evidence on the safety and efficacy of convalescent plasma for the treatment of hospitalized patients is of low or very low certainty.[803] A National Institutes of Health clinical trial evaluating the safety and efficacy of convalescent plasma in treating emergency department patients who developed mild to moderate symptoms has been halted. An interim analysis of the trial data determined that while convalescent plasma caused no harm, it was unlikely to benefit this group of patients.[804]

Baricitinib

Baricitinib is an oral Janus kinase inhibitor. It is thought to prevent the dysregulated production of proinflammatory cytokines in patients with severe or critical disease. Baricitinib is already approved in some countries for certain conditions. It has been granted an emergency-use authorization in the US, in combination with remdesivir, for the treatment of suspected or confirmed disease in hospitalized children ages 2 years and older and adults who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[805] It has not been authorized for this indication in the UK or Europe. The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for or against the use of baricitinib, in combination with remdesivir, for the treatment of hospitalized patients in cases where corticosteroids can be used instead.[439] In rare cases where corticosteroids cannot be used, the panel recommends baricitinib in combination with remdesivir for the treatment of hospitalized, nonintubated patients who require oxygen supplementation. The panel recommends against the use of baricitinib monotherapy, except in the context of a clinical trial. There are insufficient data to recommend either for or against the use of baricitinib in combination with corticosteroids. The Infectious Diseases Society of America recommends baricitinib with remdesivir in hospitalized patients with severe disease who cannot receive corticosteroids because of a contraindication, rather than remdesivir alone.[702] The combination should only be given with a corticosteroid in the context of a clinical trial. Evidence is emerging. Emergency-use authorization was based on a randomized, double-blind, placebo-controlled trial that found baricitinib plus remdesivir reduced time to recovery (defined as either being discharged from the hospital, or being hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care) within 29 days after initiating treatment compared with patients who received placebo plus remdesivir. The median time to recovery was 7 days for baricitinib plus remdesivir and 8 days for placebo plus remdesivir.[806] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Ivermectin

Ivermectin is a broad-spectrum antiparasitic agent. It has been shown to be effective against SARS-CoV-2 in vitro.[807] Ivermectin is already approved in some countries for parasitic infections, but is off-label for this indication. The European Medicines Agency does not recommend ivermectin for the treatment or prevention of COVID-19 outside of clinical trials.[808] The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of ivermectin.[439] The Infectious Diseases Society of America recommends against the use of ivermectin in outpatients and hospitalized patients outside of the context of a clinical trial, adding that more trials of sufficient design are needed.[702] Evidence is limited. The results of several randomized trials and retrospective cohort studies have been published or made available as preliminary reports (not peer reviewed as yet). Some studies showed no benefits or worsening of disease after ivermectin use; others reported a shorter time to symptom resolution, shorter time to viral clearance, greater reduction in inflammatory markers, and lower mortality rates in patients who received ivermectin compared with patients who received placebo or remdesivir. Results from adequately powered, well-designed, and well-conducted clinical trials are needed.[439] A systematic review and meta-analysis found that adding ivermectin to usual care led to significant clinical improvement and a significant reduction in all-cause mortality compared with usual care; however, the quality of evidence was very low.[809] A small randomized controlled trial found that among adults with mild disease, a 5-day course of ivermectin did not significantly improve time to resolution of symptoms compared with placebo; however, the study had important limitations and larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes.[810] Consult local drug
Coronavirus disease 2019 (COVID-19) Management

Coronavirus disease 2019 (COVID-19) management formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Anakinra

Anakinra is an intravenous/subcutaneous interleukin-1 inhibitor. It is being trialed in patients for the treatment of SARS-CoV-2-induced cytokine release syndrome. Anakinra is already approved in some countries for certain conditions, but is off-label for this indication. The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of anakinra.[439] The UK National Institute for Health and Care Excellence states that there is no evidence available to determine whether anakinra is effective, safe, or cost-effective for treating adults and children with secondary hemophagocytic lymphohistiocytosis triggered by SARS-CoV-2 or a similar coronavirus.[811] Evidence is limited. A small retrospective study found that the addition of high-dose anakinra to noninvasive ventilation and standard care (including hydroxychloroquine and lopinavir/ritonavir) in patients with moderate to severe acute respiratory distress syndrome and hyperinflammation was associated with a higher survival rate at 21 days.[812] A large retrospective study found that anakinra was associated with a significant reduction in mortality in hospitalized patients compared with patients who did not receive interleukin inhibitors.[813] A small prospective cohort study found that anakinra significantly reduced the need for invasive mechanical ventilation and mortality in patients with severe disease.[814] A small retrospective case series found that anakinra could be beneficial in patients with cytokine release syndrome when initiated early after the onset of acute hypoxic respiratory failure.[815] A phase 3 trial comparing anakinra with optimized standard of care in hospitalized patients has been suspended due to excess mortality in the intervention arm.[816] An open-label randomized controlled trial found that anakinra did not improve outcomes in patients with mild to moderate disease.[817] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Regdanvimab

Regdanvimab (formerly known as CT-P59) is an investigational neutralizing monoclonal antibody with activity against SARS-CoV-2. Regdanvimab has been granted a conditional marketing authorization in South Korea for the treatment of adults with mild symptoms who are ages ≥60 years or have at least one underlying medical condition, and all adults with moderate symptoms. The European Medicines Agency is currently reviewing the data. Evidence is limited. According to a press release from the manufacturer, regdanvimab reduced progression from mild-moderate to severe disease by 50%, and from moderate to severe disease by 68%. However, results from the phase 2/3 trial are yet to be published.[818] Regdanvimab has also demonstrated neutralizing capability against key emerging mutations, including the B.1.1.7 variant.[819]

Intravenous immune globulin

Intravenous immune globulin (IVIG) is a blood product prepared from serum pooled from healthy donors. It has an immunomodulatory effect that suppresses a hyperactive immune response. IVIG is already approved in some countries for certain conditions, but is off-label for this indication. The US National Institutes of Health guidelines panel recommends against the use of non-SARS-CoV-2-specific IVIG except in the context of a clinical trial.[439] Evidence is limited. A retrospective study of 58 patients with severe disease found that IVIG, when used as an adjuvant treatment within 48 hours of admission, may reduce the use of mechanical ventilation, reduce hospital/intensive care unit stay, and reduce 28-day mortality; however, this study had several limitations.[820] There is currently insufficient evidence to recommend IVIG.[821] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Stem cell therapy

Mesenchymal stem cells are an investigational product and have been studied for their immunomodulatory properties. It is thought that they can reduce the pathologic changes that occur in the lungs, and inhibit the cell-mediated immune inflammatory response.[822] Mesenchymal stem cells are not approved for this indication. The US National Institutes of Health guidelines panel recommends against the use of mesenchymal stem cells except in the context of a clinical trial.[439] Evidence is limited. Remestemcel-
L (ex vivo cultured adult human mesenchymal stem cells from the bone marrow of healthy adult donors) is currently in phase 3 trials for the treatment of moderate to severe acute respiratory distress syndrome in ventilator-dependent patients. An interim analysis of data found that the trial is not likely to meet its 30-day mortality reduction end point and has stopped enrollment, although the trial will be completed with the patients currently enrolled, with follow-up as planned.[823]

Interferons

Interferons are a family of cytokines with antiviral properties. Interferons are already approved in some countries for certain conditions, but are off-label for this indication. The US National Institutes of Health guidelines panel recommends against the use of interferons for the treatment of severe or critically ill patients except in the context of a clinical trial.[439] Evidence is limited. The WHO Solidarity trial found that interferon beta-1a appears to have little or no effect on hospitalized patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[781] A randomized, placebo-controlled, phase 2 trial found that nebulized interferon beta-1a was associated with a higher odds of clinical improvement and more rapid recovery.[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] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing these drugs.

Vitamin D

Vitamin D supplementation has been associated with a reduced risk of acute respiratory infections such as influenza.[827] [828] [829] [830] The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for or against vitamin D.[439] The UK National Institute for Health and Care Excellence recommends vitamin D supplementation in adults (including pregnant and breastfeeding women), young people, and children over 4 years of age between October and early March (and at other times of the year if at risk of vitamin D deficiency) to maintain bone and muscle health. However, it does not recommend supplementation to solely prevent or treat COVID-19, except as part of a clinical trial.[831] Evidence is limited. There is currently no evidence to recommend vitamin D for the prophylaxis or treatment of COVID-19.[832] A meta-analysis found that there may be a potential role for vitamin D supplementation in reducing disease severity, but noted that additional evidence is required.[833] A pilot randomized controlled trial found that high-dose calcifediol significantly reduced the need for intensive care unit treatment in hospitalized patients, and may improve clinical outcomes.[834]

Vitamin C

Vitamin C supplementation has shown promise in the treatment of viral infections.[835] High-dose intravenous vitamin C is being trialed in some centers for the treatment of severe disease.[836] The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for or against vitamin C for the treatment of noncritically ill or critically ill patients.[439] Evidence is limited. There is no evidence to support or refute the use of vitamin C in the treatment of patients with COVID-19; however, several trials are ongoing.[837] A pilot randomized controlled trial found high-dose intravenous vitamin C may show potential benefit in improving oxygenation and reducing mortality in critically ill patients; however, the trial was underpowered.[838]

Colchicine

Colchicine is an anti-inflammatory agent that downregulates multiple pro-inflammatory pathways. It is thought that its inhibitory effects on neutrophil activity, cytokine generation, and the inflammation/thrombosis interface, along with an overall lack of evidence for systemic immunosuppression, make it a useful treatment.[839] Colchicine is already approved in some countries for indications such as gout and familial Mediterranean fever, but is off-label for this indication. The UK Medicines and Healthcare products Regulatory Agency states that colchicine should not be used except in the context of a clinical trial, or unless there is an additional licensed indication for its use.[840] Evidence is limited. Studies are inconclusive in patients with mild to moderate disease, and adverse effects are significant.[841] More randomized controlled trials are required. Colchicine was being studied in the RECOVERY trial; however, recruitment has now closed as an interim analysis of the trial data found no convincing evidence that further recruitment
would provide conclusive proof of mortality benefit. A systematic review and meta-analysis found that colchicine was associated with a reduction in disease severity and mortality, especially when given early in the course of disease (within 3-6 days from the onset of symptoms or hospital admission). However, the analysis was largely based on observational studies and only included three randomized clinical trials. Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing these drugs.

**Antibiotics**

Azithromycin is a macrolide antibiotic, and doxycycline is a tetracycline antibiotic. Both are approved for use in various bacterial infections. The UK Medicines and Healthcare products Regulatory Agency recommends that azithromycin and doxycycline should not be used within primary care (or hospitalized patients for azithromycin) unless there are additional indications for which their use remains appropriate. Evidence does not support the use of these drugs. The WHO also strongly recommends against the use of hydroxychloroquine or chloroquine, regardless of disease severity. This recommendation is based on low- to moderate-certainty evidence. The US National Institutes of Health guidelines panel recommends against the use of hydroxychloroquine or chloroquine except in the context of a clinical trial. The Infectious Diseases Society of America also recommends against the use of hydroxychloroquine or chloroquine, regardless of disease severity. This recommendation is based on low- to moderate-certainty evidence. Evidence does not support the use of lopinavir/ritonavir for prevention of COVID-19. A systematic review and network meta-analysis found that lopinavir/ritonavir has little or no effect on laboratory-confirmed infection, but probably increased adverse events leading to discontinuation. Azithromycin and doxycycline should not be used within primary care (or hospitalized patients for azithromycin) unless there are additional indications for which their use remains appropriate. Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing these drugs.

**Lopinavir/ritonavir**

Lopinavir/ritonavir is an oral protease inhibitor. It is approved for the treatment of HIV infection, but is off-label for this indication. The World Health Organization strongly recommends against the use of lopinavir/ritonavir, regardless of disease severity. This recommendation is based on low- to moderate-certainty evidence. The US National Institutes of Health guidelines panel recommends against the use of lopinavir/ritonavir except in the context of a clinical trial. The Infectious Diseases Society of America also recommends against the use of lopinavir/ritonavir based on moderate-certainty evidence. Evidence does not support the use of this drug. The WHO Solidarity trial found that lopinavir/ritonavir appears to have little or no effect on hospitalized patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. The UK RECOVERY trial found that there is no beneficial effect of lopinavir/ritonavir in hospitalized patients, with no significant difference in 28-day mortality, risk of progression to mechanical ventilation or death, or duration of hospital stay between the two treatment arms (lopinavir/ritonavir versus usual care alone). A systematic review and meta-analysis found that lopinavir/ritonavir had no significant advantage in efficacy over standard care, no antivirals, or other antiviral treatments. Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

**Hydroxychloroquine/chloroquine**

Hydroxychloroquine and chloroquine are oral disease-modifying antirheumatic drugs with anti-inflammatory and immunomodulatory effects. These drugs have been shown to be effective against SARS-CoV-2 in vitro. Hydroxychloroquine and chloroquine are already approved in some countries for certain conditions, but are off-label for this indication. The World Health Organization (WHO) strongly recommends against the use of hydroxychloroquine or chloroquine, regardless of disease severity, based on low- to moderate-certainty evidence. The WHO also strongly recommends against the use of hydroxychloroquine for prevention of COVID-19. A systematic review and network meta-analysis found that hydroxychloroquine had a small or no effect on mortality and admission to hospital. There was a small or no effect on laboratory-confirmed infection, but probably increased adverse events leading to discontinuation. The US National Institutes of Health guidelines panel recommends against the use of hydroxychloroquine or chloroquine in hospitalized patients. The panel recommends against the use of both drugs in nonhospitalized patients, except in the context of a clinical trial. The panel recommends against the use of hydroxychloroquine for postexposure prophylaxis. The Infectious Diseases Society of America strongly recommends against the use of hydroxychloroquine or chloroquine in hospitalized patients based on moderate-certainty evidence. Evidence does not support the use of these drugs for treatment.
A Cochrane review found that hydroxychloroquine has no clinical benefit in hospitalized patients, with moderate- to high-certainty evidence from several randomized trials, and a probable increase in adverse events associated with its use. Evidence for prevention of hospital admission in outpatients is very uncertain. Evidence for pre- or postexposure prophylaxis is limited.[854] A living systematic review concluded that there is low-strength evidence from trials and cohort studies that hydroxychloroquine has no positive effect on all-cause mortality or the need for mechanical ventilation. Trials show low strength of evidence for no positive effect on intubation or death and discharge from the hospital, whereas evidence from cohort studies about these outcomes remains insufficient. Data are insufficiently strong to support a treatment benefit of hydroxychloroquine for other outcomes (e.g., intensive care unit admission, symptom resolution). In trials where hydroxychloroquine is initiated in the outpatient setting, there is low strength of evidence that it reduces hospitalization; however, there is insufficient evidence from cohort studies.[855] [856] The WHO Solidarity trial found that hydroxychloroquine appears to have little or no effect on hospitalized patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[781] The UK RECOVERY trial found that hydroxychloroquine does not reduce the risk of death at 28 days compared with usual care.[857] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing these drugs.

Clinical trials

Various other treatments are in clinical trials around the world. [Global coronavirus COVID-19 clinical trial tracker] (https://www.covid-trials.org/) 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. The RECOVERY Trial is currently testing these treatments: aspirin; baricitinib; dimethyl fumarate; and casirivimab/imdevimab. [RECOVERY trial] (https://www.recoverytrial.net/) [WHO: “Solidarity” clinical trial for COVID-19 treatments] (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

- Vaccines are available under temporary emergency use or conditional marketing authorizations in various countries. This is not a full marketing authorization or approval.

- Immunization programs generally prioritize people who are at highest risk from serious disease or death (e.g., residents and staff in care homes, older people, healthcare workers, and those with underlying health conditions). However, priorities differ between countries and you should consult local guidance.

- It is unknown whether vaccines prevent asymptomatic infection or transmission from individuals who are infected despite vaccination. Vaccinated people should continue to follow public health recommendations. Safety and efficacy, including duration of immunity, beyond 2 months is unknown. Advice will be updated as information on the impact of vaccination on virus transmission and indirect protection in the community is assessed.[337] [338] [339] [340] [341] [342]

- Protection starts around 14 days after vaccination, and vaccination may not protect all vaccine recipients.

- In the US, the Centers for Disease Control and Prevention recommends that people who have been vaccinated do not need to quarantine after exposure to a person with COVID-19 provided they meet the following criteria: they have been fully vaccinated and at least 2 weeks have passed since the second dose in a 2-dose series or at least 2 weeks have passed since the dose of a single-dose vaccine; they are within 3 months of their last dose in the series; and they have remained asymptomatic since their current exposure.[343]

- Emerging unpublished evidence suggests real-world efficacy in reducing the rate of infection, disease severity, hospitalization, and asymptomatic infection; however, these studies have not been peer reviewed or published as yet and further research is required.[344] [345] [346] [347]
Management

• Surveillance of adverse events is extremely important, and may reveal additional, less frequent serious adverse events not detected in clinical trials.

• For example, the Pandemrix® vaccine used during the 2009-2010 swine flu pandemic was withdrawn from the market due to an association with narcolepsy.[348]

• The new authorized mRNA vaccines have not been authorized for use in humans previously, so there is no long-term safety and efficacy data available for these types of vaccines.

• Laboratory-confirmed cases of COVID-19 have been reported after vaccination. Symptoms can be mistaken for vaccine-related adverse effects in the initial days after vaccination. Have a high level of suspicion of reported symptoms and avoid dismissing complaints as vaccine-related until vaccine recipients are tested and true infection is ruled out.[349]

• Report all suspected adverse reactions via your local reporting system.

  • US: [Vaccine Adverse Event Reporting System (VAERS)] (https://vaers.hhs.gov/)
  • International: [WHO: Adverse Event Following Immunization (AEFI) form] (http://investigation.gvsi-aefi-tools.org/#step-1)

• Vaccine dose schedules may differ across locations.

  • There have been suggestions about extending the length of time between doses, reducing the number of doses, changing the dose (half-dose), or mixing and matching different COVID-19 vaccines in order to vaccinate more people. However, there is no evidence to support these strategies as yet.[350]

  • The World Health Organization (WHO) recommends that countries experiencing exceptional epidemiologic circumstances may consider delaying the administration of the second dose of mRNA vaccines for a short period (up to 42 days based on currently available clinical trial data) as a pragmatic approach to maximizing the number of individuals benefiting from a first dose while vaccine supply continues to increase. However, evidence for this extension is not strong. Countries should ensure that any such program adjustments to dose intervals do not affect the likelihood of receiving the second dose. The WHO does not support altering doses.[339] [340]

  • In the UK, the Joint Committee on Vaccination and Immunisation recommends that delivery of the first dose of any vaccine to as many eligible individuals as possible should be initially prioritized over delivery of a second dose.[351] [352] However, there is a lack of evidence to support an extended dose interval between the first and second dose, and this is outside of the manufacturer's authorized dose recommendations.[353]

  • In the US, the Centers for Disease Control and Prevention recommends that the second dose of an mRNA vaccine can be scheduled for up to 6 weeks after the first dose if the recommended dosing interval cannot be met. The agency continues to emphasize that the second dose should be given as close to the recommended interval as possible, and states that the two mRNA vaccines that are available in the US may be considered interchangeable in exceptional circumstances.[354]

  • Clinical trials have started in the UK to determine whether different vaccines may be used for the 2-dose regimen.[355]

  • Consult local guidelines before administering vaccines. Patients must give free and voluntary informed consent prior to vaccination.[356]

• The tables below compare the vaccines that have been authorized for use in the US.

  • In addition to these, the AstraZeneca COVID-19 vaccine (a chimpanzee adenovirus vector vaccine that carries the genetic code for the severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] spike protein) has been authorized in many countries, CoronaVac® and Sinopharm® (inactivated version of the SARS-CoV-2 virus) have been authorized in China, and Sputnik V® (an adenovirus vector vaccine) has been authorized in Russia and is 91.6% effective.[357]

  • Several other vaccine candidates are still in development including mRNA vaccines, DNA vaccines, viral vector vaccines, protein subunit vaccines, live-attenuated vaccines, inactivated virus vaccines, and intranasal delivery systems.[358]
Coronavirus disease 2019 (COVID-19)

**Management**

- [WHO: draft landscape and tracker of COVID-19 candidate vaccines](https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines)

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### mRNA vaccines

<table>
<thead>
<tr>
<th></th>
<th>Pfizer/BioNTech</th>
<th>Moderna</th>
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<tbody>
<tr>
<td><strong>Vaccine type</strong></td>
<td>Lipid nanoparticle-formulated mRNA vaccine that encodes the SARS-CoV-2 spike protein</td>
<td></td>
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<tr>
<td><strong>Overall efficacy</strong></td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≥16 years of age</td>
<td>≥18 years of age</td>
</tr>
<tr>
<td><strong>Authorized dose</strong> **</td>
<td>TWO-DOSE REGIMEN</td>
<td>TWO-DOSE REGIMEN</td>
</tr>
<tr>
<td></td>
<td>0.3 mL (30 mcg) IM; second dose at least 21 days after</td>
<td>0.5 mL (100 mcg) IM; second dose at least 28 days after</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Hypersensitivity to active substance or any excipients; immediate allergic reaction to first dose (should not get second dose)</td>
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<td><strong>Cautions</strong></td>
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<td>Acute severe febrile illness</td>
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<td>Bleeding disorders or anticoagulation</td>
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<td>Immunocompromised</td>
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<td>Pregnancy and breastfeeding</td>
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<td></td>
<td>Previous treatment with COVID-19 monoclonal antibodies/plasma</td>
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<tr>
<td><strong>Adverse events</strong> **</td>
<td><strong>Common</strong>: headache; arthralgia; myalgia; injection-site reactions; fatigue; fever; chills; nausea; vomiting; diarrhea; rash; lymphadenopathy</td>
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<tr>
<td></td>
<td><strong>Uncommon</strong>: malaise; acute peripheral facial paralysis; anaphylaxis; hypersensitivity; face swelling (if dermatologic fillers present)</td>
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<tr>
<td><strong>Interactions</strong></td>
<td>Interactions with other vaccines/drugs have not been studied (WHO recommends at least 14 days between COVID-19 vaccines and others)</td>
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**Comparison of selected authorized mRNA COVID-19 vaccines. Data is evolving; consult local drug formulary or guidelines for detailed information for your location.**  
*Data based on phase 3 clinical trials - see Vaccine efficacy clinical trial data and Vaccine safety clinical trial data sections below for detailed information.**  
**Dose schedules may differ in some locations. Last reviewed/updated: 24 March 2021**

BMJ Best Practice editorial team; compiled using data from the UK product information
<table>
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<th>Viral vector vaccines</th>
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<td><strong>Vaccine type</strong></td>
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<tr>
<td><strong>Overall efficacy</strong></td>
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<tr>
<td><strong>Age</strong></td>
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<td><strong>Authorized dose</strong></td>
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<tr>
<td><strong>Contraindications</strong></td>
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<td><strong>Interactions</strong></td>
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**Comparison of selected authorized viral vector COVID-19 vaccines.** Data is evolving; consult local drug formulary or guidelines for detailed information for your location. *Data based on phase 3 clinical trials - see Vaccine efficacy clinical trial data and Vaccine safety clinical trial data sections below for detailed information. **Dose schedules may differ in some locations. Last reviewed/updated: 24 March 2021

**BMJ Best Practice editorial team; compiled using data from the US product information**

**Vaccines and thromboembolic events**

- Thromboembolic events have been reported in a small number of people after vaccination. As a consequence, several countries temporarily suspended use of the AstraZeneca COVID-19 vaccine in early March 2021.
• The European Medicines Agency’s safety committee completed a preliminary review of this safety signal and has confirmed that the benefits of the vaccine continue to outweigh the risks.[359]

• Overall, the number of thromboembolic events reported after vaccination, both in studies before licensing and in reports after rollout of vaccination campaigns, was lower than that expected in the general population.

• Based on this, the committee confirmed that the vaccine is not associated with an increase in the overall risk of thromboembolic events.

• The committee also confirmed that there is no evidence of a problem related to specific batches of the vaccine or to particular manufacturing sites.

• However, the committee did find that the vaccine may be associated with very rare cases of blood clots associated with thrombocytopenia, including rare cases of mesenteric vein or cerebral vein/cerebral venous sinus thrombosis. Most cases were reported in women under the age of 55 years. The number of reported events exceeded those expected, and while causality has not been confirmed, it cannot be excluded. The strength of any association is uncertain.

• Therefore, the committee advises that healthcare professionals should be alert for possible cases of thromboembolism, disseminated intravascular coagulation, or cerebral venous sinus thrombosis after vaccination. Recipients should be warned to seek immediate medical attention for symptoms of thromboembolism and thrombocytopenia, particularly in the 3 days after vaccination.

• The UK Medicines and Healthcare products Regulatory Agency has also confirmed that the benefits of the AstraZeneca vaccine outweigh the risks following a detailed review. A review into five cases of cerebral venous sinus thrombosis (occurring together with thrombocytopenia) reported in the UK is ongoing.[360]

• The World Health Organization also considers the benefits of the AstraZeneca vaccine to outweigh the risks, and recommends that vaccinations continue.[361]

• Despite these findings, the Norwegian Institute of Public Health will keep use of the AstraZeneca vaccine on hold in Norway as it continues its review of the situation.[362]

• The European Medicines Agency has also started a review of a safety signal to assess reports of immune thrombocytopenia.[363]

Vaccines and anaphylaxis or vasovagal reactions

• Severe allergic reactions, including anaphylaxis, have been reported outside of clinical trials in the general population after vaccination.

• In the US, monitoring by the VAERS detected 4.7 cases of anaphylaxis per million doses of the Pfizer/BioNTech vaccine, and 2.5 cases per million doses of the Moderna vaccine as of 18 January 2021.[364]

• In the UK, monitoring of the Yellow Card reporting system detected 223 cases of anaphylaxis with the Pfizer/BioNTech vaccine, and 234 cases of anaphylaxis with the AstraZeneca vaccine as of 7 March 2021.[365]

• It has been suggested that reactions after vaccines may be due to the presence of lipid pegylated ethylene glycol (PEG), or PEG derivatives such as polysorbates.[366]

• The WHO recommends that a history of anaphylaxis to any component of the vaccine is a contraindication to vaccination for all vaccines. People with an immediate anaphylactic allergic reaction to the first dose of two-dose regimens should not receive additional doses. Administer vaccines only in settings where anaphylaxis can be treated, and observe for at least 15 minutes after vaccination.[339] [340] [341] [342]

• The WHO recommends people with an immediate nonanaphylactic allergic reaction to the first dose of an mRNA vaccine (i.e. urticaria, angioedema, or respiratory symptoms such as cough, stridor, or wheezing without any other symptoms within 4 hours of administration) should not receive additional doses unless recommended after review by a health professional with specialist expertise. A history of any immediate allergic reaction to any other vaccine or
Injectable therapy is considered a precaution, but not a contraindication, to vaccination. Perform a risk assessment to determine the type and severity of reaction and the reliability of the information. These people may still be vaccinated, but the risks should be weighed against the benefits of vaccination, and the recipient should be observed for 30 minutes after vaccination in healthcare settings where anaphylaxis can be treated immediately. Anaphylactic reactions have also been reported in people without a history of severe allergic reactions. Food, insect venom, contact, or seasonal allergies, and allergic rhinitis, eczema, and asthma are not considered a precaution. There is no contraindication or precaution to vaccination for people with latex, egg, or gelatin allergies.

- The UK-based Medicines and Healthcare products Regulatory Agency recommends that anyone with a previous history of allergic reactions to the ingredients of the vaccine should not receive it, but those with any other allergies such as a food allergy can have the vaccine.
- In the US, the Centers for Disease Control and Prevention recommends that people with a contraindication to one type of the currently authorized vaccines (e.g., an mRNA vaccine) have a precaution to the other (e.g., viral vector vaccine). However, because of potential cross-reactive hypersensitivity between ingredients in mRNA and viral vector vaccines, an allergist/immunologist should be consulted to help determine whether the patient can safely receive vaccination.
- Guidelines on vaccinating people with a history of allergy or anaphylaxis may differ across locations; consult local guidance.
- People with a history of receiving dermal fillers may develop swelling at or near the site of filler injection (e.g., lips, face) following administration of an mRNA vaccine. This appears to be temporary and may be treated with corticosteroids. The European Medicines Agency has started a review of a safety signal to assess reports of localized swelling related to dermal fillers.
- Delayed-onset local reactions around the injection site have been reported (median 8 days after first vaccination), and are sometimes quite large (e.g., at least 10 cm in diameter).
- Anxiety-related reactions, including vasovagal reactions and hyperventilation, may occur. Ensure precautions are in place to avoid injury from fainting.

Vaccines and specific patient populations

- There are limited or no data available from clinical trials about the use of vaccines in specific patient populations. Despite this, the WHO recommends that the following populations may be vaccinated, depending on the vaccine used:
  - Older people (without an upper age limit)
  - People with comorbidities that have been identified as increasing the risk for severe disease
  - Immunocompromised people who are part of a group recommended for vaccination
  - People living with HIV who are part of a group recommended for vaccination
  - People with autoimmune conditions who have no contraindications to vaccination and who are part of a group recommended for vaccination
  - People with a history of Bell palsy who have no contraindications to vaccination
  - People with a history of symptomatic or asymptomatic SARS-CoV-2 infection.

- Delayed vaccination is recommended in people with an acute febrile illness or current acute COVID-19 (until they are afebrile and have recovered from acute illness), and in people who previously received passive antibody therapy for COVID-19 (for at least 90 days).
- Delayed vaccination may be considered in people who have had confirmed SARS-CoV-2 infection in the preceding 6 months (until near the end of this period).
- A single dose of an mRNA vaccine has been found to elicit a rapid immune response in seropositive participants, with post-vaccination antibody titers that were similar to (or exceeded) titers found in seronegative participants who received two vaccinations.
People with previous infection have been shown to generate strong humoral and cellular responses to one dose of the Pfizer/BioNTech COVID-19 vaccine with evidence of high titers of in vitro live virus neutralization.[370]

A preprint study found that one dose of the vaccine may be sufficient for people who have already been infected with SARS-CoV-2; however, further research is required.[371]

The WHO recommends an individual risk–benefit assessment for very frail older persons with a life expectancy anticipated to be less than 3 months.[340] The Norwegian Medicines Agency recommends conducting more thorough evaluations of very frail older patients before vaccination, after 23 patients died shortly after receiving the Pfizer/BioNTech vaccine. However, it is currently unknown whether there is a connection between these deaths and the vaccine. The agency has investigated 13 of the deaths so far and has concluded that common adverse reactions of mRNA vaccines, such as fever, nausea, and diarrhea, may have contributed to fatal outcomes in some of the frail patients.[372] [373]

Emerging data suggest that vaccine efficacy may be lower in cancer patients and solid organ transplant recipients; however, further research is required.[374] [375]

Vaccines and pregnant/breastfeeding women

- Use caution in pregnant and breastfeeding women as there are no safety and efficacy data available.

Clinical trials in pregnant women have started for some vaccines.

- The WHO recommends not using vaccines in pregnant women, unless the benefits outweigh the potential risks (e.g., healthcare workers at high risk of exposure, women with comorbidities that place them in a high-risk group for severe disease). It recommends that women who are breastfeeding, and who are part of a group recommended for vaccination, should be offered vaccination on an equivalent basis. It does not recommend delaying pregnancy or discontinuing breastfeeding after vaccination.[339] [340] [341] [342]

- Public Health England recommends that pregnant women should not routinely be vaccinated; however, vaccination may be considered when the potential benefits outweigh the potential risks for the mother and fetus.[376] It recommends that women who are breastfeeding can receive the vaccine.[377]

- The American College of Obstetricians and Gynecologists recommends that COVID-19 vaccines should not be withheld from pregnant or breastfeeding women who meet criteria for vaccination based on recommended priority groups. Discuss the risks and benefits with the person before vaccination. Pregnant and breastfeeding women who decline vaccination should be supported in their decision.[378]

Vaccine efficacy clinical trial data

- Pfizer/BioNTech COVID-19 vaccine

Efficacy is based on an interim analysis of results from a phase 3 trial of 43,448 participants (with randomization to vaccine and placebo arms in a 1:1 ratio). The vaccine is reported to be 95% effective in preventing symptomatic COVID-19 after 2 doses compared with placebo (saline), in people ages 16 years and older. This is based on an analysis of 170 confirmed cases of COVID-19 with an onset at least 7 days after the second dose among recipients with no evidence of existing or prior SARS-CoV-2 infection (8 cases in the vaccine arm versus 162 cases in the placebo arm). Efficacy was 52% after the first dose. Among 10 cases of severe disease with onset after the first dose, 9 cases occurred in the placebo arm and 1 case occurred in the vaccine arm. This only provides preliminary evidence of vaccine-mediated protection against severe disease.[337]

The vaccine appears to be over 90% effective in the real-world setting according to an analysis of Israel’s mass vaccination campaign. Estimated efficacy at least 7 days after the second dose was 92% for documented infection, 94% for symptomatic disease, 87% for hospitalization, and 92% for severe disease.[379] It has also been found to reduce the number of patients ≥70 years of age requiring mechanical ventilation by 67% between October-December 2020 to February 2021.[380]

Preliminary studies suggest that the vaccine may be effective against new SARS-CoV-2 variants with spike protein mutations (i.e.,B.1.1.7 and B.1.351 lineages and N501Y mutations); however,
neutralization of the B.1.351 variant may be weaker.[381] [382] [383] [384] [385] Further research is required.

- The manufacturer has started testing whether a third dose (booster) is safe and effective against currently circulating and emerging SARS-CoV-2 variants.[386]

- **Moderna COVID-19 vaccine**

  - Efficacy is based on an interim analysis of results from a phase 3 trial of 30,420 participants (with randomization to vaccine and placebo arms in a 1:1 ratio). The vaccine is reported to be 94.1% effective in preventing symptomatic COVID-19 after 2 doses compared with placebo (saline) in people ages 18 years and older. This is based on an analysis of 196 confirmed cases of COVID-19 with an onset at least 14 days after the second dose among recipients with no evidence of existing or prior SARS-CoV-2 infection (11 cases in the vaccine arm versus 185 cases in the placebo arm). Among 30 cases of severe disease (including one fatality) with onset after the first dose, all cases occurred in the placebo arm and none in the vaccine arm.[387]

  - Preliminary studies suggest that the vaccine may be effective against new SARS-CoV-2 variants with spike protein mutations (i.e., B.1.351 and B.1.1.7 lineages). Although neutralizing antibody titers were lower for the B.1.351 variant compared with earlier SARS-CoV-2 variants, levels were expected to be protective, although this is yet to be confirmed.[384] [388] [389] Further research is required. The manufacturer will test an additional booster dose to study the ability to further increase neutralizing titers against emerging strains beyond the existing primary vaccination series. It has also started phase 2 clinical trials of a variant booster candidate against the B.1.351 lineage variant (known as mRNA-1273.351).[390]

- **AstraZeneca COVID-19 vaccine**

  - Efficacy is based on an interim analysis of pooled data from four ongoing randomized controlled clinical trials with 11,636 participants conducted in the UK, Brazil, and South Africa. The vaccine is reported to be 70.4% effective in preventing symptomatic COVID-19 after 2 doses compared with control (meningococcal vaccine or saline) in people ages 18 years and older. This is based on an analysis of 131 confirmed cases of COVID-19 with an onset at least 15 days after the second dose among recipients with no evidence of existing or prior SARS-CoV-2 infection (30 cases in the vaccine arm versus 101 cases in the placebo arm). Trial results are yet to be published. Among 2 cases of severe disease, all cases occurred in the control arm and none in the vaccine arm. Efficacy and safety data are currently limited in people ≥65 years of age.[391]

  - Vaccine efficacy appears to be higher when the interval between doses is longer. Data from a primary analysis of the clinical trials were consistent with those seen in the interim analysis, and includes results of a further month of data collection with 332 cases of symptomatic disease reported. The study found that a single standard dose provides 76% protection overall against symptomatic disease in the first 90 days after vaccination. Efficacy reached 80% after the second dose in those with a dosing interval of 12 weeks or more. However, the efficacy was only 55.1% if the two doses were given less than 6 weeks apart.[392] The WHO recommends an interval of 8 to 12 weeks between doses.[341]

  - Data from the US phase 3 trial has been reported by the manufacturer. Based on an interim analysis of 32,449 participants and 141 symptomatic cases, vaccine efficacy at preventing symptomatic disease has been reported as 79%. [393] However, the National Institutes of Health has queried the accuracy of the data.[394]

  - A preprint study suggests that the vaccine may be effective against symptomatic infection caused by the B.1.1.7 SARS-CoV-2 variant.[395] However, a randomized controlled trial found that a two-dose regimen did not show protection against mild to moderate disease due to the B.1.351 variant, reporting an efficacy rate of 21.9%.[396]

- **Janssen COVID-19 vaccine**

  - Efficacy is based on an interim analysis of pooled data from an ongoing randomized controlled clinical trial with 43,783 participants conducted in South Africa, South America, Mexico, and the US. The vaccine is reported to be 66.9% and 66.1% effective in preventing moderate to severe/critical disease at least 14 days and 28 days after vaccination, respectively, compared with placebo (saline) in people ages 18 years and older. Efficacy for prevention of severe/critical disease was 76.7% and 85.4% at least 14 days and 28 days after vaccination, respectively.
These figures are based on an analysis of 464 confirmed cases of COVID-19 with an onset at least 14 days after vaccination among recipients with no evidence of existing or prior SARS-CoV-2 infection (116 cases in the vaccine arm versus 348 cases in the placebo arm), and 259 confirmed cases of COVID-19 with an onset at least 28 days after vaccination (66 cases in the vaccine arm versus 193 cases in the placebo arm). Vaccine efficacy was higher in the US (74%) compared with South Africa (52%). Trial results are yet to be published.[397]

Vaccine safety clinical trial data

- **Pfizer/BioNTech COVID-19 vaccine**
  - Safety is based on an interim analysis of results from a phase 3 trial of 43,448 participants. The reactogenicity subset included 8183 participants.[337]
  - Local adverse reactions were more common in the vaccine group compared with placebo, with the most common reaction being injection-site pain within 7 days after injection (83% after the first dose and 78% after the second dose in younger participants; 71% after the first dose and 66% after the second dose in older participants). Less than 1% of participants reported severe pain. Local adverse reactions were similar after the first and second doses.
  - Systemic adverse reactions were more common in the vaccine group compared with placebo, and were reported more often by younger patients and after the second dose. The most commonly reported systemic adverse reactions after the second dose were fatigue (59% in younger participants; 51% in older participants), headache (52% in younger participants; 39% in older participants), and fever (16% in younger participants; 11% in older participants). Severe systemic events were reported in <2% of participants after either dose, except for fatigue and headache after the second dose.
  - Other rare adverse events included lymphadenopathy, shoulder injury (related to vaccine administration), paroxysmal ventricular arrhythmia, and right leg paresthesia.

- **Moderna COVID-19 vaccine**
  - Safety is based on an interim analysis of results from a phase 3 trial of 30,420 participants.[387]
  - Solicited local and systemic adverse reactions were reported in 87.8% of participants within 7 days after the first dose in the vaccine group compared with 48% in the placebo group, and 92.2% of participants within 7 days after the second dose in the vaccine group compared with 42.8% in the placebo group. The most commonly reported solicited adverse reactions included injection-site reactions, fatigue, headache, myalgia, and arthralgia. These reactions were more commonly reported and were more severe after the second dose. Solicited adverse reactions were more common among participants ages 18 to 64 years compared with adults ages ≥65 years.
  - Unsolicited adverse events related to vaccination (up to 28 days after any injection) were reported in 8.2% of participants in the vaccine group compared with 4.5% in the placebo group. The incidence of severe adverse events was higher in the vaccine group compared with the placebo group (0.5% versus 0.2%). The most commonly reported unsolicited adverse events (reported in at least 1% of participants) were fatigue and headache. The relative incidence of these events was not affected by age.
  - Bell palsy occurred more commonly in the vaccine group (three cases) compared with the placebo group (one case), suggesting that it may be more than a chance event. This will require close monitoring as larger populations are vaccinated outside of clinical trials.

- **AstraZeneca COVID-19 vaccine**
• Safety is based on an interim analysis of pooled data from four ongoing randomized controlled clinical trials with 23,745 participants conducted in the UK, Brazil, and South Africa (trial results are yet to be published).[398]

• The most frequently reported adverse events were: injection-site reactions (>60%); headache, fatigue (>50%); myalgia, malaise (>40%); fever, chills (>30%); arthralgia, nausea (>20%). Adverse reactions were milder and reported less frequently after the second dose and in adults ages ≥65 years.

Janssen COVID-19 vaccine

• Safety is based on an interim analysis of pooled data from an ongoing randomized controlled clinical trial with 43,783 participants conducted in South Africa, South America, Mexico, and the US (trial results are yet to be published). The reactogenicity subset included 6736 participants.[397]

• The most frequently reported adverse events were: injection-site reactions (48.6%); headache (38.9%); fatigue (38.2%); and myalgia (33.2%). Approximately 0.7% and 1.8% of local and systemic solicited adverse reactions, respectively, were reported as grade 3. Reports of solicited reactions were less common among participants ≥60 years of age. Other adverse reactions possibly related to the vaccine included urticaria, thromboembolic events, and tinnitus. One serious event of a hypersensitivity reaction (not classified as anaphylaxis) and one case of severe systemic reactogenicity were likely related to the vaccine.

Vaccine trial limitations

• A key limitation of the data is the short duration of safety and efficacy follow-up. Trials were not sufficiently powered to detect less common adverse events reliably, and the median follow-up time was only 2 months after the second dose. Trials do not address whether the vaccine prevents transmission or affects infectiousness, and the duration of protection is yet to be determined. There are no data on children or younger adolescents, pregnant or breastfeeding women, or immunocompromised people.

• There are concerns that the trials were not designed to detect a reduction in any serious outcome such as hospital admissions, use of intensive care, or deaths, or whether the vaccines can interrupt transmission of the virus – two key primary end points in vaccine efficacy trials.[399] Also, since the trials have been published, important questions about final efficacy data exclusions, as well as concerns about the use of pain and fever medications, unblinding, and primary event adjudication committees have been raised.[400]

• Planned long-term follow-up of participants is unlikely to occur in the context of trials due to the ethics of following a placebo recipient long-term without offering the vaccine. This could inadvertently threaten ongoing vaccine research that is yet to define immunologic correlates of protection against COVID-19, which could vary according to the vaccine platform, individual characteristics, age groups, and population subset.[401] [402] [403]

• Previous trials of coronavirus vaccines identified cellular immunopathology and antibody-dependent enhancement (ADE) as potential safety issues. There are concerns over ADE of SARS-CoV-2 due to subsequent exposure to wild-type SARS-CoV-2 post vaccination and prior exposure to other coronaviruses (such as those that cause the common cold).[404] [405] Available data do not indicate a risk of vaccine-enhanced disease with the mRNA vaccines; however, data are limited and the risk over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further.[337] [387]

Infection prevention and control for healthcare professionals

• Always consult local infection prevention and control protocols; only basic principles are detailed here.
• Immediately isolate all suspected or confirmed cases in an area that is separate from other patients. Place patients in adequately ventilated single rooms if possible. When single rooms are not available, place all cases together in the same room and ensure there is at least 3 feet (1 meter) between patients.[406]

• Implement standard precautions at all times:[406]
  • Practice hand and respiratory hygiene
  • Give patients a medical mask to wear
  • Wear appropriate personal protective equipment
  • Practice safe waste management and environmental cleaning.

• Implement additional contact and droplet precautions before entering a room where cases are admitted:[406]
  • Wear a medical mask, gloves, an appropriate gown, and eye/facial protection (e.g., goggles or a face shield)
  • Use single-use or disposable equipment.

• Implement airborne precautions when performing aerosol-generating procedures, including placing patients in a negative pressure room.[406]
  • 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.[406]

• Appropriate personal protective equipment gives healthcare workers a high level of protection against COVID-19. A cross-sectional study of 420 healthcare workers deployed to Wuhan with appropriate personal protective equipment tested negative for SARS-CoV-2 on molecular and serologic testing when they returned home, despite all participants having direct contact with COVID-19 patients and performing at least one aerosol-generating procedure.[407] Standard surgical masks are as effective as respirator masks for preventing infection of healthcare workers in outbreaks of viral respiratory illnesses such as influenza, but it is unknown whether this applies to COVID-19.[408]

• Detailed infection prevention and control guidance is available:

Telehealth for primary care physicians

• It is important that primary care physicians avoid in-person assessment of patients with suspected COVID-19 in primary care when possible to avoid infection.[409] Most patients can be managed remotely by telephone or video consultations. Algorithms for dealing with these patients are available:
  • [BMJ: covid-19 – a remote assessment in primary care] (https://www.bmj.com/content/368/bmj.m1182)

General prevention measures for the general public

• People should be advised to:[410] [411]
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- Wash hands often with soap and water for at least 20 seconds or an alcohol-based hand sanitizer (that contains at least 60% alcohol), especially after being in a public place, blowing their nose, or coughing/sneezing. Avoid touching the eyes, nose, and mouth with unwashed hands.

- Avoid close contact with people (i.e., maintain a distance of at least 3 feet [1 meter]) including shaking hands, particularly those who are sick, have a fever, or are coughing or sneezing. Avoid going to crowded and poorly ventilated places. It is important to note that recommended distances differ between countries (for example, 6 feet [2 meters] is recommended in the US and UK) and you should consult local guidance. However, there is no evidence to support a distance of 6 feet (2 meters).[412]

- Practice respiratory hygiene (i.e., cover mouth and nose when coughing or sneezing, discard tissue immediately in a closed bin, and wash hands).

- Seek medical care early if they have a fever, cough, and difficulty breathing, and share their previous travel and contact history (travelers or suspected/confirmed cases) with their healthcare provider.

- Stay at home and self-isolate if they are sick, even with mild symptoms, until they recover (except to get medical care).

- Clean and disinfect frequently touched surfaces daily (e.g., light switches, door knobs, countertops, handles, phones).

  - [BMJ Learning: Covid-19 – handwashing technique and PPE videos] (https://www.youtube.com/playlist?list=PLVnZu1tqPoT1GIgDciRjTs6ep9ySVxE)
  - [Centre for Evidence-Based Medicine: what is the evidence to support the 2-metre social distancing rule to reduce COVID-19 transmission?] (https://www.cebm.net/covid-19/what-is-the-evidence-to-support-the-2-metre-social-distancing-rule-to-reduce-covid-19-transmission/)

### Face masks in community settings

- Recommendations on the use of face masks in community settings vary between countries.[413] It is mandatory to wear a mask in public in certain countries or in certain situations, and masks may be worn in some countries according to local cultural habits. Consult local public health guidance for more information.

- There is no high-quality or direct scientific evidence to support the widespread use of masks by healthy people in the community setting, and there are risks and benefits that must be considered. Data on effectiveness is based on limited and inconsistent observational and epidemiologic studies.[91] The first randomized controlled trial to investigate the efficacy of masks in the community (in addition to other public health measures such as social distancing) found that the recommendation to wear surgical masks when outside the home among others did not reduce incident SARS-CoV-2 infection compared with no mask recommendation. However, the study did not assess whether masks could decrease disease transmission from mask wearers to others.[414] A Cochrane review found that wearing a mask may make little to no difference in how many people caught influenza-like illnesses; however, this is based on low-certainty evidence, and does not include results of studies from the current COVID-19 pandemic.[415] Evidence for mask effectiveness for respiratory tract infection prevention is stronger in healthcare settings compared with community settings; direct evidence on comparative effectiveness in SARS-CoV-2 infection is insufficient. The strength of evidence for any mask use versus nonuse in community settings is low.[416] Randomized trials have not addressed the question of source control.

- Despite the lack of good-quality evidence, the WHO advises that in areas of known or suspected community or cluster transmission, people should wear a nonmedical mask in the following circumstances: indoor or outdoor settings where physical distancing cannot be maintained; indoor
settings with inadequate ventilation, regardless of whether physical distancing can be maintained; and in situations when physical distancing cannot be maintained and the person has a higher risk of severe complications (e.g., older age, underlying condition). Caregivers and those living with suspected or confirmed cases should wear a medical mask when in the same room, regardless of whether the case has symptoms. Children ages up to 5 years should not wear masks for source control. A risk-based approach is recommended for children ages 6 to 11 years. Special considerations are required for immunocompromised children, or children with certain diseases, developmental disorders, or disabilities. The WHO advises that people should not wear masks during vigorous-intensity physical activity. Use of a mask alone is insufficient to provide adequate protection, and they should be used in conjunction with other infection prevention and control measures such as frequent hand hygiene and social distancing.\[91\]

- Potential harms and disadvantages of wearing masks include: potential increased risk of self-contamination due to manipulation of face mask and touching face/eyes, or when nonmedical masks are not changed when wet or soiled; headache and/or breathing difficulties; facial skin lesions, irritant dermatitis, or worsening acne; discomfort; difficulty communicating; social and psychological acceptance; false sense of security; poor compliance; waste management issues; and difficulties for patients with chronic respiratory conditions or breathing problems.\[91\] Masks may also create a humid habitat where the virus can remain active and this may increase viral load in the respiratory tract; deeper breathing caused by wearing a mask may push the virus deeper into the lungs.\[418\] There are insufficient data to quantify all of the adverse effects that might reduce the acceptability, adherence, and effectiveness of face masks.\[419\]

- Cloth masks have limited efficacy in preventing viral transmission compared with medical-grade masks.\[420\] Efficacy depends on the type of material used, the number of layers, the degree of moisture in the mask, and the fitting of the mask on the face. In a study comparing the use of cloth masks to surgical masks in healthcare workers, the rates of all infection outcomes were highest in the cloth mask arm, with the rate of influenza-like illness statistically significantly higher in this group. Moisture retention, reuse of cloth masks, and poor filtration may result in increased risk of infection.\[421\]

- [BMJ: facemasks for the prevention of infection in healthcare and community settings] (https://www.bmj.com/content/350/bmj.h694)

**Alcohol-based hand sanitizers**

- The Centers for Disease Control and Prevention has issued a warning about alcohol-based sanitizers containing methanol (which may be labeled as containing ethanol). Methanol poisoning should be considered in patients who present with relevant signs and symptoms (e.g., headache, impaired vision, nausea/vomiting, abdominal pain, loss of coordination, decreased level of consciousness) who report ingestion of hand sanitizer or frequent repeated topical use. Cases of permanent blindness and death have been reported.\[422\]

- Frequent use of hand sanitizers may result in antimicrobial resistance. Accidental ingestion and unintentional ocular exposures, especially by children, have also been reported.\[423\] \[424\]

**Travel-related control measures**

- Many countries have implemented travel-related control measures including complete closure of borders, partial travel restrictions, entry or exit screening, and/or quarantine of travelers. Overall, low to very low evidence suggests that travel-related control measures may help to limit the spread of infection across national borders. Cross-border travel restrictions are likely to be more effective than entry and exit screening, and screening is likely to be more effective in combination with other measures (e.g., quarantine, observation).\[425\]

- Entry/exit screening: people traveling from areas with a high risk of infection may be screened using questionnaires about their travel, contact with ill persons, symptoms of infection, and/or measurement of their temperature. Low-certainty evidence suggests that screening at travel hubs may slightly slow the importation of infected cases; however, the evidence base comes from two mathematical model studies and is limited by their assumptions. Evidence suggests that one-time screening in apparently healthy people may miss between 40% and 100% of people who are infected, although the certainty of this ranges from very low to moderate. In very low-prevalence settings, screening for symptoms or temperature may result in few false negatives and many true negatives, despite low overall accuracy. Repeated screenings may result in more cases being identified eventually and reduced harm from
false reassurance.[426] Entry screening at three major US airports found a low yield of laboratory-diagnosed cases (one case per 85,000 travelers) between January and September 2020.[427]

• Quarantine: enforced quarantine is being used to isolate easily identifiable cohorts of people at potential risk of recent exposure. Despite limited evidence, a Cochrane review found quarantine to be important in reducing the number of people infected and deaths, especially when started earlier and when used in combination with other prevention and control measures. However, the current evidence is limited because most studies are based on mathematical modeling studies that make assumptions on important model parameters.[428] The psychosocial effects of enforced quarantine may have long-lasting repercussions.[429] [430]

• Travelers who arrive in the UK are required to self-isolate for 10 days unless they have traveled from an exempt country. Travelers who have visited a country with a travel ban in the 10 days before arrival must self-isolate, along with their household, for 10 days from the day of departure from these countries. [Public Health England: how to quarantine when you arrive in England] (https://www.gov.uk/guidance/how-to-quarantine-when-you-arrive-in-england)

Social distancing

• Many countries have implemented mandatory social distancing measures in order to reduce and delay transmission (e.g., city lockdowns, stay-at-home orders, curfews, nonessential business closures, bans on gatherings, school and university closures, travel restrictions and bans, remote working, quarantine of exposed people).

• Although the evidence for social distancing for COVID-19 is limited, it is emerging, and the best available evidence appears to support social distancing measures to reduce the transmission and delay spread. The timing and duration of these measures appears to be critical.[431] [432] When comparing countries with more restrictive nonpharmaceutical interventions (e.g., mandatory stay-at-home and business closure orders) to countries with less restrictive nonpharmaceutical interventions, implementing any nonpharmaceutical interventions was associated with a significant reduction in case growth. 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. It should be noted that the study has important limitations.[433]

• Researchers in Singapore found that social distancing measures (isolation of infected individuals and family quarantine, school closures, and workplace distancing) significantly decreased the number of infections in simulation models.[434]

• Harms must also be considered. Public health policies mostly rely on models and these models often ignore potential harms including excess death and inequalities arising from economic damage, negative health effects, and effects on vulnerable populations.[435] Negative consequences of community-based mass quarantine include psychological distress, food insecurity, economic challenges, diminished healthcare access, heightened communication inequalities, alternative delivery of education, and gender-based violence.[436]

Shielding extremely vulnerable people

• Shielding is a measure used to protect vulnerable people (including children) who are at very high risk of severe illness from COVID-19 because they have an underlying health condition. Shielding involves minimizing all interactions between those who are extremely vulnerable and other people to protect them from coming into contact with the virus.

• Extremely vulnerable groups include:[437]
  
  • Solid organ transplant recipients
  • People with specific cancers
  • People with severe respiratory conditions (e.g., cystic fibrosis, severe asthma, or severe COPD)
  • People with rare diseases that significantly increase the risk of infections (e.g., homozygous sickle cell disease, severe combined immunodeficiency)
  • People on immunosuppression therapies sufficient to significantly increase the risk of infection
  • People with spleen problems (e.g., prior splenectomy)
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- Adults with Down syndrome
- Adults on dialysis or with chronic kidney disease
- Women who are pregnant with significant heart disease (congenital or acquired)
- Other people who have also been classed as clinically extremely vulnerable based on clinical judgment and an assessment of their needs.

- The UK government recommends that clinically extremely vulnerable people are urged to follow specific precautions based on current public health restrictions until 31 March 2021, after which those on the shielded list can begin to follow national restrictions for the general population:

- Consult current guidance for specific recommendations (recommendations may differ between countries).
- Shielding advice for children and young adults is available. Consult current guidance for specific recommendations (recommendations may differ between countries).
  - [Royal College of Paediatrics and Child Health: COVID-19 – guidance on clinically extremely vulnerable children and young people](https://www.rcpch.ac.uk/resources/covid-19-shielding-guidance-children-young-people)

Lifestyle modifications

- Lifestyle modifications (e.g., smoking cessation, weight loss) may help to reduce the risk of COVID-19, and may be a useful adjunct to other interventions.[438]

Pre-exposure or postexposure prophylaxis

- There are no drugs recommended for pre-exposure prophylaxis or postexposure prophylaxis, except in the context of a clinical trial.[439] See the Emerging section for more information.

Immunity passports

- Some governments are discussing or implementing certifications for people who have contracted and recovered from COVID-19 based on antibody tests (sometimes called "immunity passports"). Possession of a passport would allow people to have a greater range of privileges (e.g., work, education, travel). However, the WHO does not support these certifications as there is currently no evidence that people who have recovered from infection and have antibodies are protected from reinfection.[440] Other potential issues include lack of public support for these measures, potential for discrimination of groups of people, testing errors (including cross-reactivity with other human coronaviruses), access to testing, fraud, legal and ethical objections, and people getting infected intentionally in order to obtain a certification.[441]

Patient discussions

General discussions
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- Communicate with patients and their families and caregivers, and support their mental wellbeing to help alleviate any anxiety and fear they may have. Signpost to charities and support groups.[478]
- 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, malgla, sore throat, drowsiness (particularly in older people), poor appetite, and chest discomfort/pain. Additional symptoms in children may include grunting, nasal flare, nasal congestion, poor appetite, gastrointestinal symptoms, skin rash, and conjunctivitis. The presence of fever, rash, abdominal pain, diarrhea, or vomiting in children may indicate pediatric inflammatory multisystem syndrome (PIMS). Reassure the patient that they are likely to feel much better in a week if their symptoms are mild.[478]
- Discuss who to contact if their symptoms get worse, or if PIMS is suspected. Offer telephone or video consultations as appropriate.[478]
- 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.[478]

General prevention measures

- Wash hands often with soap and water for at least 20 seconds or an alcohol-based hand sanitizer (that contains at least 60% alcohol), especially after being in a public place, blowing your nose, or coughing/sneezing. Avoid touching the eyes, nose, and mouth with unwashed hands.
- Avoid close contact with people (i.e., maintain a distance of at least 3 feet [1 meter]) including shaking hands, particularly those who are sick, have a fever, or are coughing or sneezing. Avoid going to crowded and poorly ventilated places. It is important to note that recommended distances differ between countries (for example, 6 feet [2 meters] is recommended in the US and UK) and you should consult local guidance.
- Practice respiratory hygiene (i.e., cover mouth and nose when coughing or sneezing, discard tissue immediately in a closed bin, and wash hands).
- Stay at home if you are sick, even with mild symptoms, until you recover (except to get medical care)
- Clean and disinfect frequently touched surfaces daily (e.g., light switches, door knobs, countertops, handles, phones).[410] [411]

Face masks

- Despite the lack of good-quality evidence, the World Health Organization (WHO) advises that in areas of known or suspected community or cluster transmission, people should wear a nonmedical mask in the following circumstances: indoor or outdoor settings where physical distancing cannot be maintained; indoor settings with inadequate ventilation, regardless of whether physical distancing can be maintained; and situations when physical distancing cannot be maintained and the person has a higher risk of severe complications (e.g., older age, underlying condition). Caregivers and those living with suspected or confirmed cases should wear a medical mask when in the same room, regardless of whether the case has symptoms. Children ages up to 5 years should not wear masks for source control. A risk-based approach is recommended for children ages 6 to 11 years. Special considerations are required for immunocompromised children, or children with certain diseases, developmental disorders, or disabilities. The WHO advises that people should not wear masks during vigorous-intensity physical activity. Use of a mask alone is insufficient to provide adequate protection, and they should be used in conjunction with other infection prevention and control measures such as frequent hand hygiene and social distancing.[91]
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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=IfnYJd4lKus&t=141s)

Travel advice

- Many countries have implemented international travel bans/closed their borders, have issued advice for domestic travel. Some countries are restricting entry to foreign nationals who have been to affected areas in the preceding 14 days, or are enforcing quarantine periods (e.g., at home or in a designated facility such as a medi-hotel) where the person’s health and infection status are closely monitored. Some countries are requiring a negative test before departure and after arrival, and are implementing travel measures to protect against new international variants of the virus. Masks may be mandatory on flights.
  - Consult local guidance for specific travel restriction recommendations in your country:
    - [NaTHNaC: travel health pro] (https://travelhealthpro.org.uk/)
    - [UK Department for Transport] (https://www.gov.uk/government/organisations/department-for-transport)

Pets and animals

- At this time, there is no evidence that companion animals (including pets and other animals) play a significant role in the spread of COVID-19, and the risk of animals spreading COVID-19 to people is considered to be very low. There is no evidence that the virus can spread to people from the skin or fur of companion animals.[1093]
- A very small number of pets have been reported to be infected with the virus after close contact with people with confirmed COVID-19; however, thousands of pets have been tested in the US with none testing positive. There is evidence that cats and ferrets are highly susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, while dogs and other livestock have no or low susceptibility. Large cats in captivity (lions, tigers, and a puma) and domestic pet cats have tested positive after contact with symptomatic humans. Transmission between cats has also been reported. The virus has been reported in mink on farms, and once the virus is introduced on
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a farm, can spread between mink, and between mink and other animals on the farm. There is also the possibility that mink may transmit the infection to humans in these environments.[1094] [1095] [1096] [1097] [1098] Gorillas in a US zoo have tested positive. It is suspected that the gorillas acquired the infection from an asymptomatic staff member.[1099]

- Advise patients to limit their contact with their pets and other animals, especially while they are symptomatic. Advise people to not let pets interact with people or animals outside the household, and if a member of the household becomes unwell to isolate them from everyone else, including pets.[1100]

**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.[1101]
- Guidance on return to sports after COVID-19 in children is available from the American Academy of Pediatrics:

**Resources**

Coronavirus disease 2019 (COVID-19) Follow up

Monitoring

Regularly monitor the following in hospitalized patients to facilitate early recognition of deterioration and monitor for complications:[136] [740]

- Vital signs (temperature, respiratory rate, heart rate, blood pressure, oxygen saturation)
- Hematologic and biochemistry parameters
- Coagulation parameters (D-dimer, fibrinogen, platelet count, prothrombin time)
- ECG
- Chest imaging
- Signs and symptoms of venous or arterial thromboembolism.

Medical early warning scores

- Utilize medical early warning scores that facilitate early recognition and escalation of treatment of deteriorating patients (e.g., National Early Warning Score 2 [NEWS2], Pediatric Early Warning Signs [PEWS]) where possible.[136]
- There are no data on the value of using these scores in patients with COVID-19 in the primary care setting.[1076]
- 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.[1077]

Pregnant women

- Monitor vital signs three to four times daily and fetal heart rate in pregnant women with confirmed infection who are symptomatic and admitted to hospital. Perform fetal growth ultrasounds and Doppler assessments to monitor for potential intrauterine growth restriction in pregnant women with confirmed infection who are asymptomatic.[749] Perform fetal growth ultrasound 14 days after resolution of symptoms.[751]

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.[136]
- 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.[1078]
- More than half of patients discharged from hospital had lung function and chest imaging abnormalities 12 weeks after symptom onset.[1079] Pulmonary function tests may reveal altered diffusion capacity, a restrictive pattern, or an obstructive pattern.[1080]

Prognostic scores in development

- Various prognostic and clinical risk scores are being researched or developed for COVID-19; however, further external validation across various populations is needed before their use can be recommended. The World Health Organization recommends using clinical judgment, including consideration of the patient’s values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the intensive care unit, rather than currently available prediction models for prognosis.[136]

- A-DROP: a modified version of CURB-65 that showed better accuracy of in-hospital death prediction on admission in patients with COVID-19 pneumonia compared with other widely used community-acquired pneumonia scores.[1081]
• APACHE II: an effective clinical tool to predict hospital mortality that performed better than SOFA and CURB-65 scores in patients with COVID-19. A score of 17 or more is an early indicator of death and may help provide guidance to make further clinical decisions.[1082]

• CALL: a risk factor scoring system that scores patients based on four factors: comorbidities, age, lymphocyte count, and lactate dehydrogenase level. One study found that 96% of patients with low CALL scores did not progress to severe disease.[1083]

• COVID-GRAM: a web-based calculator that estimates the probability that a patient will develop critical illness and relies on the following 10 variables at admission: chest radiographic abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin. Additional validation studies, especially outside of China, are required.[1084]

• COVID-19MRS: a rapid, operator-independent clinical tool that was found to objectively predict mortality in one retrospective cohort study.[1085]

• COVID-19 SEIMC: a mortality prediction score for predicting 30-day mortality of patients attending hospital emergency departments, based on age, low age-adjusted SaO₂, neutrophil-to-lymphocyte ratio, estimated glomerular filtration rate, dyspnea, and sex. It has been externally validated with two large datasets from patients hospitalized with laboratory-confirmed disease and shows a high degree of accuracy.[1086]

• QCOVID: a novel clinical risk prediction algorithm to estimate the risk of hospital admission and mortality based on age, ethnicity, deprivation, body mass index, and a range of comorbidities. A population-based cohort study found that the algorithm performed well, showing very high levels of discrimination for deaths and hospital admissions.[1087] The risk model is being used in the UK to help clinicians identify adults with multiple risk factors that make them more vulnerable to COVID-19, and inform decisions about vaccination cohorts and shielding.[1088]

• SCARP: a novel risk calculator that provides clinically meaningful predictions of whether hospitalized patients will progress to severe illness or death based on variables that are readily available (e.g., pulse oximetry, oxygen supplementation, respiratory rate, pulse). The calculator has undergone internal and temporal validation, but further studies are required.[1089]

• SOARS: a five-predictor risk prediction score based on demographic and clinical characteristics (i.e., SpO₂, obesity, age, respiratory rate, stroke history). May be useful to identify patients who have a low probability of mortality for outpatient monitoring and management, and could potentially be used to inform clinical triage in preadmission settings. Further validation is required.[1090]

• 3F: a mortality prediction model based on three clinical features: age, minimum oxygen saturation, and type of patient encounter (i.e., inpatient vs outpatient and telehealth encounters). One study found that the model showed high accuracy when applied to retrospective and prospective data sets of COVID-19 patients.[1091]

• 4C: a score developed and validated in a UK prospective cohort study of adults admitted to hospital with COVID-19. The score uses patient demographics, clinical observations, and blood parameters commonly available at the time of hospital admission, and can accurately characterize patients as being at low, intermediate, high, or very high risk of death. The score outperformed other risk stratification tools, showed clinical decision-making utility, and had similar performance to more complex models.[1092]

• [The BMJ 10-minute consultation: what is my covid risk?] (https://www.bmj.com/content/372/bmj.n637)
Complications

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<tr>
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<tr>
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Early reports suggest that COVID-19 patients treated in the intensive care unit can present with post-intensive care syndrome, a spectrum of psychiatric, cognitive, and/or physical disability (e.g., muscle weakness, cognitive dysfunction, insomnia, depression, anxiety, post-traumatic stress disorder, delirium, encephalopathy) that affects survivors of critical illness, and persists after the patient has been discharged from the intensive care unit. Weakness affects 33% of patients who receive mechanical ventilation, 50% of patients with sepsis, and <50% of patients who remain in the intensive care unit for more than 1 week. Cognitive dysfunction affects 30% to 80% of patients. The risk can be minimized with medication management, physical rehabilitation, family support, and follow-up clinics.[439]

venous thromboembolism                     | variable  | high       |

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.[947] COVID-19 patients with thromboembolic events have 1.93 times the odds of dying compared with patients without venous thromboembolism.[948]

Coagulopathy in COVID-19 has a prothrombotic character, which may explain reports of thromboembolic complications.[949] Patients may be predisposed to venous thromboembolism due to the direct effects of COVID-19, or the indirect effects of infection (e.g., severe inflammatory response, critical illness, traditional risk factors).[950] Thrombotic events may be due to cytokine storm, hypoxic injury, endothelial dysfunction, hypercoagulability, and/or increased platelet activity.[951]

The risk factors with the most evidence for being predictive of venous thromboembolism are older age and elevated D-dimer levels.[952] Patients with very high D-dimer levels have the greatest risk of thrombosis and may benefit from active monitoring.[601] [602]

If venous thromboembolism is suspected, perform a computed tomographic angiography or ultrasound of the venous system of the lower extremities.[953]

Treat patients with a thromboembolic event (or who are highly suspected to have thromboembolic disease if imaging is not possible) with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19. There are currently insufficient data to recommend either for or against using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19. Patients who require extracorporeal membrane oxygenation or continuous renal replacement therapy, or who have thrombosis of catheters or extracorporeal filters, should be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19.[439]

Initial parenteral anticoagulation with a low molecular weight heparin or unfractionated heparin is preferred in acutely ill hospitalized patients; however, direct oral anticoagulants may be used provided there is no potential for drug-drug interactions (lead-in therapy with a parenteral anticoagulant is required for dabigatran and edoxaban). Warfarin can be used after overlap with initial parenteral anticoagulation. Parenteral anticoagulation with a low molecular weight heparin or fondaparinux is preferred over unfractionated heparin in critically ill patients. Direct oral anticoagulants are the preferred option in outpatients provided there is no potential for drug-drug interactions, with warfarin considered a suitable alternative. Anticoagulation therapy is recommended for a minimum of 3 months. Thrombolytic therapy is recommended in select patients with pulmonary embolism.[689]

The American Society of Hematology has published draft guideline recommendations on the use of anticoagulation in patients with COVID-19.[954]
Coronavirus disease 2019 (COVID-19) Follow up

Complications | Timeframe | Likelihood
---|---|---
A high incidence (14.7%) of asymptomatic deep vein thrombosis was reported in a cohort of patients with COVID-19 pneumonia. An autopsy study of 12 patients revealed deep vein thrombosis in 58% of patients in whom venous thromboembolism was not suspected before death. These studies highlight the importance of having a high suspicion for venous thromboembolism in patients who have signs of coagulopathy, including elevated D-dimer level.

While these patients are at higher risk of thrombotic events, they may also be at an elevated risk for bleeding. In a small retrospective study, 11% of patients at high risk of venous thromboembolism also had a high risk of bleeding.

Antiphospholipid antibodies and lupus anticoagulant have been detected in a small number of critically ill patients. The presence of these antibodies can rarely lead to thrombotic events in some patients (especially those who are genetically predisposed) that are difficult to differentiate from other causes of multifocal thrombosis. In other patients, antiphospholipid antibodies may be transient and disappear within a few weeks. The significance of this finding is unknown, although it is thought that these antibodies may not be involved in the pathogenesis of venous thromboembolism in patients with severe COVID-19. Anticoagulation should be considered in these patients.

It has been suggested that a new term (e.g., COVID-19-associated pulmonary thrombosis, diffuse pulmonary intravascular coagulopathy, or microvascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome [MicroCLOTS]) be used rather than the term pulmonary embolism as it has been hypothesized that the pathophysiology is different; local thrombi are formed in the lung vessels due to a local inflammatory process rather than the classical emboli coming from elsewhere in the body. However, this has not become accepted practice.

Cases of arterial thrombosis, cerebral venous thrombosis, and acute limb ischemia secondary to thrombosis have been reported. The prevalence of arterial thromboembolism appears to be substantial at 3.9%; however, evidence is limited.

Cardiovascular complications variable high

COVID-19 is associated with a high inflammatory burden that can result in cardiovascular complications with a variety of clinical presentations. Inflammation in the myocardium can result in myocarditis, heart failure, arrhythmias, acute coronary syndrome, rapid deterioration, and sudden death. These complications can occur on presentation or develop as the severity of illness worsens. It is uncertain to what extent acute systolic heart failure is mediated by myocarditis, cytokine storm, small vessel thrombotic complications, microvascular dysfunction, or a variant of stress-induced cardiomyopathy.

Cardiovascular complications have been reported in 14.1% of patients during hospitalization, with an overall case fatality rate of 9.6%. Patients with preexisting cardiovascular comorbidities or risk factors are at higher risk for cardiovascular complications and mortality. Complications include arrhythmias or palpitations (18.4%), myocardial injury (10.3%), angina (10.2%), acute myocardial infarction (3.5%), and acute heart failure (2%). Cases of fulminant myocarditis, cardiac tamponade, cor pulmonale, takotsubo syndrome, and pericarditis have also been reported. A Cochrane review found that the most common cardiovascular complications were cardiac arrhythmias, heart failure, and arterial and venous occlusive events.

Laboratory biomarkers may help identify those at greater risk of developing cardiovascular complications and of death. Elevated cardiac biomarkers and emerging arrhythmia are associated with the development of severe disease and the need for intensive care admission.

Prevalence of cardiac disease is high among patients who are severely or critically ill, and these patients usually require intensive care and have a poor prognosis and higher rate of in-hospital mortality. These patients are more likely to require noninvasive or invasive ventilation, and have a higher risk of thromboembolic events and septic shock compared with patients without a history of cardiac disease.
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.[478]

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.[478]

Seek specialist cardiology advice on treatment and follow local treatment protocols. There are limited data to recommend any specific drug treatments for these patients. Management should involve a multidisciplinary team including intensive care specialists, cardiologists, and infectious disease specialists.[974] It is important to consider that some drugs may prolong the QT interval and lead to arrhythmias. Guidelines for the management of COVID-19-related myocarditis are available.[986] Infection may have longer-term implications for overall cardiovascular health; however, further research is required.[987] A study of 100 patients who had recently recovered from COVID-19 found that cardiovascular magnetic resonance imaging revealed ongoing myocardial inflammation in 60% of patients, independent of preexisting conditions, severity and overall course of the acute illness, and time from the original diagnosis.[988]

### acute kidney injury

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The pooled incidence of acute kidney injury is 10.6%, which is higher than the incidence in hospitalized patients without COVID-19. Patients with acute kidney injury have a significantly increased risk of in-hospital mortality (odds ratio of 11.05). The mortality rate and incidence in patients in China was significantly lower than those in patients outside of China. Risk factors include older age ≥60 years, male sex, and severe infection.[989]

In a small UK cohort, 29% of hospitalized children met the diagnostic criteria for acute kidney injury, with most cases occurring in children admitted to the intensive care unit and in those with pediatric inflammatory multisystem syndrome.[990]

Can develop at any time before, during, or after hospital admission. 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).[478] Direct kidney infection has been confirmed in an autopsy study of a single patient.[991]

Follow local guidelines for assessing and managing acute kidney injury. Continuous renal replacement therapy (CRRT) is recommended in critically ill patients with acute kidney injury who develop indications for renal replacement therapy; prolonged intermittent renal replacement therapy is recommended over hemodialysis if CRRT is not available or possible.[439]

Monitor patients with chronic kidney disease for at least 2 years after acute kidney injury.[478]

Cases of nephritis and collapsing glomerulopathy have been reported.[992] [993]

### acute liver injury

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Liver injury may be associated with preexisting liver disease, viral infection, drug toxicity, systemic inflammation, hypoxia, or hemodynamic issues; however, the underlying mechanism is unclear. The overall prevalence is 25%, although there is no uniform definition of liver injury in these patients and prevalence depends on the definition used in studies. The overall prevalence may be as low as 9% when strict criteria for diagnosis are used. The prevalence of elevated alanine aminotransferase and aspartate transaminase.
Complications | Timeframe | Likelihood
--- | --- | ---
aminotransferase is 19% and 22%, respectively. The prevalence of hypertransaminasemia is higher in patients with severe disease compared with patients with nonsevere disease.[994]
Risk factors associated with severe liver injury include older age, preexisting liver disease, and severe COVID-19.[995]
Medications used in the treatment of COVID-19 (e.g., lopinavir/ritonavir) may have a detrimental effect on liver injury.[995]
Guidelines on the management of liver derangement in patients with COVID-19 have been published.[996]

**neurologic complications**
variable | medium

Patients commonly have central or peripheral neurologic complications, possibly due to viral invasion of the central nervous system, inflammatory response, or immune dysregulation.[997]

Neurologic manifestations have been reported in 4% to 57% of patients in large retrospective observational studies. Central nervous system manifestations were more common than peripheral nervous system manifestations.[997] However, most studies included minor symptoms such as headache and dizziness, which are classified as symptoms of COVID-19 in this topic rather than complications. Neurologic complications are rare in children.[998]

Neurologic complications include acute cerebrovascular disease, impairment of consciousness, ataxia, seizures, corticospinal tract signs, meningoencephalitis, encephalopathy, encephalomyelitis, peripheral demyelinating lesions, peripheral neuropathy, intracerebral hemorrhage, cerebral venous sinus thrombosis, myopathy, myasthenia gravis, Guillain-Barre syndrome and other neuropathies, status epilepticus, and abnormal findings on brain magnetic resonance imaging.[997] [999] [1000]

Patients may present with these manifestations, or they may develop them during the course of the disease. Neurologic complications tend to develop 1 to 2 weeks after the onset of respiratory disease.[1001]

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%).[997] Stroke is relatively frequent among hospitalized COVID-19 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.[1002] [1003] Stroke presents later in severe disease, and earlier in mild to moderate disease.[1004] 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.[1005] Guidelines for the management of acute ischemic stroke in patients with COVID-19 infection have been published.[1006]

Guillain-Barre syndrome has been reported. Both post-infectious and pre-infectious patterns have been reported.[997] 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.[1007]

Patients with preexisting neurologic disorders may develop an exacerbation of their neurologic symptoms and severe COVID-19.[1008]

Patients may show cerebral changes on magnetic resonance imaging months after recovery, suggesting that long-term consequences may be possible.[1009]

Neurologic involvement is common in children and adolescents. In a case series of 1695 patients <21 years of age, 22% of patients had documented neurologic involvement. Those with neurologic involvement were more likely to have an underlying neurologic disorder compared with those without,
but a similar number were previously healthy. In the majority of cases, symptoms were transient. However, approximately 12% had life-threatening conditions including severe encephalopathy, central nervous system infection/demyelination, Guillain-Barre syndrome/variants, and acute fulminant cerebral edema.[1010]

**post-COVID-19 syndrome (long COVID)**

**Definition:** signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis. Ongoing symptomatic COVID-19 is defined as signs and symptoms from 4 weeks up to 12 weeks. The syndrome is not thought to be linked to disease severity or specific signs and symptoms during the acute phase of illness.[877]

**Epidemiology:** persistence of sequelae ranged from 14 days to 3 months from infection in previously healthy adults ages 18 to 50 years, and included persistent fatigue (39% to 73%), dyspnea (39% to 74%), decrease in quality of life (44% to 69%), impaired pulmonary function (39% to 83%), myocardiitis (3% to 26%), persistent neurologic symptoms (55%), psychiatric diagnoses (5.5%), and persistent altered sense of taste/smell (33% to 36%).[1011] In a study in Italy, nearly 90% of hospitalized patients who recovered from COVID-19 reported persistence of at least one symptom 2 months after discharge. Only 12.6% of patients had no related symptoms, 32% had one or two symptoms, and 55% had three or more symptoms.[1012] Another study in the UK found that nearly 75% of patients who are discharged from hospital remain symptomatic at 3 months.[1013] Persistent symptoms have been reported for as long as 9 months after illness, including in many outpatients with mild disease.[1014] Prolonged illness can occur among young adults with no underlying comorbidities. In a survey study of symptomatic adults, 35% had not returned to their usual state of health 2 to 3 weeks after testing. Among those ages 18 to 34 years with no underlying chronic medical conditions, 20% had not returned to their usual state of health.[1015] The number of symptoms at follow-up was associated with the symptom load during the acute phase of infection and the number of comorbidities in nonhospitalized patients.[1016] Persistent symptoms have been reported in pregnant women and children, but appear to be less common in children compared with adults.[439] [1017]

**Diagnosis:** use a holistic, person-centered approach that includes a comprehensive clinical history (including history of suspected or confirmed acute COVID-19, nature and severity of previous and current symptoms, timing and duration of symptoms since the start of acute illness, and a history of other health conditions), and appropriate examination that involves assessing physical, cognitive, psychological, and psychiatric symptoms, as well as functional abilities. Refer patients with signs or symptoms that could be caused by an acute or life-threatening complication (e.g., severe hypoxemia, signs of severe lung disease, cardiac chest pain, multisystem inflammatory syndrome in children) urgently to the relevant acute services.[877]

**Signs and symptoms:** symptoms vary widely, may relapse and remit or fluctuate, can change unpredictably, and can occur in those with mild disease only. Common long-term symptoms include persistent cough, low-grade fever, breathlessness, fatigue, pain, chest pain/tightness, palpitations, myalgia, arthralgia, headaches, vision changes, hearing loss, earache, tinnitus, sore throat, loss of taste/smell, impaired mobility, numbness in extremities, dizziness, tremors, memory loss, mood changes, skin rashes, gastrointestinal symptoms, neurocognitive difficulties, sleep disturbances, delirium (older people), and mental health conditions (e.g., anxiety, depression).[439] [877] [1018] Gastrointestinal sequelae including loss of appetite, nausea, acid reflux, and diarrhea are common in patients 3 months after discharge.[1019] Some of the symptoms may overlap with post-intensive care syndrome (see above).[439] The inability to return to normal activities, emotional and mental health outcomes, and financial loss are common.[1020]

**Investigations:** tailor investigations to the clinical presentation, and to rule out any acute or life-threatening complications and alternative diagnoses. Investigations may include blood tests (e.g., complete blood count, kidney and liver function tests, C-reactive protein, ferritin, thyroid function), oxygen saturation, blood pressure and heart rate measurements, exercise tolerance test, chest imaging, electrocardiogram, and
Complications | Timeframe | Likelihood
--- | --- | ---
psychiatric assessment.[439] [877] [1018] Approximately 50% of patients had residual abnormalities on chest CT and pulmonary function tests at 3 months.[1021] Around 9% of patients had deteriorating chest x-ray appearances at follow-up, which may indicate lung fibrosis. Persistently elevated D-dimer and C-reactive protein have also been reported.[1022]

Management: give advice and information on self-management including ways to self-manage symptoms (e.g., set realistic goals, antipyretic for fever, breathing techniques for chronic cough, home pulse oximetry for monitoring breathlessness, pulmonary rehabilitation, staged return to exercise); who to contact if there is concern about symptoms or if there is need for support; sources of support (e.g., support groups, online forums); and how to get support from other services (e.g., social care, housing, financial support). A personalized, multidisciplinary rehabilitation plan that covers physical, psychological, and psychiatric aspects of rehabilitation is an important part of management. Many patients recover spontaneously with holistic support, rest, symptomatic treatment, and a gradual increase in activity. Referral to a specialist may be required in patients where there is clinical concern along with respiratory, cardiac, or neurologic symptoms that are new, persistent, or progressive.[877] [1018]

Follow-up: agree with the patient how often follow-up and monitoring are needed (either in person or remotely), and which healthcare professionals should be involved. Take into account the patient’s level of need and the services involved. Tailor monitoring to the patient’s symptoms, and consider supported self-monitoring at home (e.g., heart rate, blood pressure, pulse oximetry). Be alert to symptoms that could require referral or investigation.[877]


[BMJ webinar: long COVID – how to define it and how to manage it] (https://www.bmj.com/content/370/bmj.m3489)

[BMJ: management of post-acute covid-19 in primary care] (https://www.bmj.com/content/370/bmj.m3026)

### Cardiac Arrest

**Cardiac arrest**

**Variable**

**Medium**

In-hospital cardiac arrest is common in critically ill patients with COVID-19, and is associated with poor survival, particularly among older patients. Among 5019 critically ill patients with COVID-19, 14% had an in-hospital cardiac arrest. Risk factors included older age, male sex, presence of comorbidities, and admission to a hospital with a smaller number of intensive care unit beds. Approximately 57% of patients received cardiopulmonary resuscitation. The most common rhythms at the time of resuscitation were pulseless electrical activity (49.8%) and asystole (23.8%). Of those who received resuscitation, 12% survived to hospital discharge with most of these patients being younger than 45 years of age.[1023]

### Septic Shock

**Septic shock**

**Variable**

**Low**

Reported in 4% to 8% of patients in case series.[49] [50] [557] [1024]

Guidelines for the management of shock in critically ill patients with COVID-19 recommend a conservative fluid strategy (crystalloids preferred over colloids) and a vasoactive agent. Norepinephrine (noradrenaline) is the preferred first-line agent, with vasopressin or epinephrine (adrenaline) considered suitable alternatives. Vasopressin can be added to norepinephrine if target mean arterial pressure cannot be achieved with norepinephrine alone.[439] [678] Low-dose corticosteroid therapy is recommended for refractory shock.[439]

### Disseminated Intravascular Coagulation

**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.[1025] The pooled incidence of DIC is 3%, and it is associated with poor...
Complications | Timeframe | Likelihood
--- | --- | ---
prognosis. The incidence was higher in patients with severe disease and those admitted to the intensive care unit, and in nonsurvivors compared with survivors.[1026]

Coagulopathy manifests as elevated fibrinogen, elevated D-dimer, and minimal change in prothrombin time, partial thromboplastin time, and platelet count in the early stages of infection. Increasing interleukin-6 levels correlate with increasing fibrinogen levels. Coagulopathy appears to be related to severity of illness and the resultant thromboinflammation. Monitor D-dimer level closely.[1027]

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.[1028] In patients with heparin-induced thrombocytopenia (or a history of it), argatroban or bivalirudin are recommended.[1025]

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.[740] [1027]

**acute respiratory failure**

variable | low

Reported in 8% of patients in case series.[50]

Leading cause of mortality in patients with COVID-19.[882]

Children can quickly progress to respiratory failure.[11]

cytokine release syndrome

variable | low

Cytokine release syndrome may cause ARDS or multiple-organ dysfunction, which may lead to death.[1029] Elevated serum proinflammatory cytokines (e.g., tumor necrosis factor alpha, interleukin-2, interleukin-6, interleukin-8, interleukin-10, granulocyte-colony stimulating factor, monocyte chemoattractant protein 1) and inflammatory markers (e.g., C-reactive protein, serum ferritin) have been commonly reported in patients with severe COVID-19. This likely represents a type of virus-induced secondary hemophagocytic lymphohistiocytosis, which may be fatal.[49] [1030] [607] [1031] Interleukin-6, in particular, has been associated with severe COVID-19 and increased mortality.[1032]

One study found that patients who require admission to the intensive care unit have significantly higher levels of interleukin-6, interleukin-10, and tumor necrosis factor alpha, and fewer CD4+ and CD8+ T cells.[1033]

However, the pooled mean serum interleukin-6 level was markedly less in patients with severe or critical COVID-19 compared with patients with other disorders associated with elevated cytokines such as cytokine release syndrome, sepsis, and non-COVID-19-related ARDS. These findings question the role of cytokine storm in COVID-19-induced organ dysfunction, and further research is required.[1034]

Cytokine release syndrome has been reported in children, although cases appear to be rare.[1035] See the section below on pediatric inflammatory multisystem syndrome.

**pediatric inflammatory multisystem syndrome**

variable | low

A rare, but severe condition, reported in children and adolescents approximately 2 to 4 weeks after the onset of COVID-19, likely due to a postinfectious inflammatory process. The syndrome has a strong temporal association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1036] [1037] [1038] Also known as PIMS, multisystem inflammatory syndrome in children (MIS-C), pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), as well as other variations.

The syndrome shares common features with Kawasaki disease and toxic shock syndrome, but case definitions vary.[446] [1038] [1039] [1040] Most patients have fever, as well as features of shock,
Coronavirus disease 2019 (COVID-19)

Follow up

Complications | Timeframe | Likelihood | Cardiac involvement (e.g., elevated cardiac markers, congestive heart failure, cardiac dysfunction, myocarditis, coronary artery dilation or aneurysm, hypotension, pericardial effusion, mitral regurgitation), gastrointestinal symptoms (e.g., abdominal pain, vomiting, diarrhea), and significantly elevated inflammatory markers. Additional clinical and laboratory characteristics including thrombocytopenia, fatigue, headache, myalgia, sore throat, and lymphadenopathy have been suggested to refine the case definition. Mucocutaneous findings may be present, many of which overlap with Kawasaki disease.

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.

A systematic review of 27 studies (913 cases) globally found that the median age of patients was 9.3 years of age, and 57% of patients were male. At least one comorbidity was reported in 31% of cases, most commonly obesity, asthma, and chronic lung disease. The most common manifestations were fever (99%), gastrointestinal symptoms (87%), and cardiovascular symptoms such as myocardial dysfunction (55%), coronary artery aneurysms (22%), and shock (66%). The pooled prevalence of respiratory symptoms was 41%, and neurologic symptoms was 36%. Other symptoms included conjunctivitis (57%), rash (59%), and oral mucosal changes (42%). Inflammatory and cardiac markers were elevated in the majority of patients, and 38% had abnormal findings on chest x-ray. Approximately 79% of patients required intensive care admission, 63% required inotropic support, 57% required anticoagulation, and 33% required mechanical ventilation. The mortality rate was 1.9%.

In the UK, 78 cases were reported across 21 pediatric intensive care units in a multicenter observational study. The median age was 11 years and 67% were male. Children from minority ethnic backgrounds accounted for 78% of cases. Fever, shock, abdominal pain, vomiting, and diarrhea were the common presenting features. Around 36% had evidence of coronary artery abnormalities. In terms of treatment, 46% required invasive ventilation and 83% required vasopressor support.

In the US, 2617 cases have been reported, with 33 deaths (as of 1 March 2021). In a US case series of 1116 patients diagnosed with MIS-C, those with MIS-C were more likely to have the following characteristics compared with patients with severe COVID-19: age 6 to 12 years; non-Hispanic Black ethnicity; cardiorespiratory involvement; cardiovascular without respiratory involvement; mucocutaneous without cardiorespiratory involvement; higher neutrophil-to-lymphocyte ratio; higher C-reactive protein level; and lower platelet count. These patterns may help differentiate between MIS-C and COVID-19. Factors associated with more severe outcomes (e.g., intensive care unit admission, decreased cardiac function, shock, myocarditis) include: age >5 years; non-Hispanic Black ethnicity; symptoms of dyspnea or abdominal pain; elevated C-reactive protein, troponin, ferritin, D-dimer, brain natriuretic peptide, or interleukin-6; and reduced lymphocyte or platelet counts.

The most common cardiovascular complications include shock, cardiac arrhythmias, pericardial effusion, and coronary artery dilatation.

Management is mainly supportive and involves a multidisciplinary team (pediatric infectious disease, cardiology, rheumatology, critical care). Patients are commonly managed with intravenous immune globulin, vasopressor support, corticosteroids, immune modulators, anticoagulation, antiplatelet therapy, and respiratory support. A national consensus management pathway from the UK is available. The American College of Rheumatology has published guidelines on the diagnosis and management of MIS-C.

While an association between this syndrome and COVID-19 seems plausible based on current evidence, the association is not definitive and further research is required. It is not clear yet whether this syndrome is Kawasaki disease with SARS-CoV-2 as the triggering agent, or whether this is a different syndrome, although increasing evidence suggests that they are two separate syndromes. The syndrome appears to occur in children who have not manifested the early stages of COVID-19, but appears similar to the later phase of COVID-19 in adults. Immunologically, PIMS appears to be a distinct clinical entity from Kawasaki disease as neutrophilia and raised monocyte counts, features of Kawasaki disease, were not observed in one cohort.
### Complications

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<th>Timeframe</th>
<th>Likelihood</th>
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<tr>
<td>Cases of MIS-C have been reported in neonates and temporally associated with prenatal exposure.</td>
<td>variable</td>
<td>low</td>
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<tr>
<td>Cases of COVID-19-associated Kawasaki-like multisystem inflammatory disease have been reported in adults.</td>
<td>variable</td>
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#### Pregnancy-related complications

Pregnancy outcome is usually good, although there are little data on exposure during early pregnancy.

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.

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 pre-pandemic period, so these preterm births could have been medically indicated.

The overall rates of stillbirths and neonatal deaths do not seem to be higher than the background rates. In England, there is no evidence of an increase in stillbirths regionally or nationally during the pandemic when compared with the same months in the previous year and despite variable community infection rates in different regions.

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.

#### Aspergillosis

Invasive pulmonary aspergillosis has been reported in critically ill patients with moderate to severe ARDS. Aspergillosis has been reported in 6% of patients admitted to the intensive care unit. A prospective observational study found that one third of mechanically ventilated patients with COVID-19 had putative invasive pulmonary aspergillosis.

Intubation for more than 7 days may be a risk factor. Other potential risk factors include older age, chronic obstructive pulmonary disease, immunosuppression, critical illness, or use of high-dose corticosteroids. Consider aspergillosis in patients who deteriorate despite optimal supportive care or have other suspicious radiologic or clinical features.

Prescribe appropriate antifungal therapy according to local guidelines. Guidance on the diagnosis and management of COVID-19-associated pulmonary aspergillosis has been published.

#### Pancreatic injury

Mild pancreatic injury (defined as elevated serum amylase or lipase levels) has been reported in 17% of patients in one case series. It is unknown whether this is a direct viral effect or due to the harmful immune response that occurs in some patients. Clinical acute pancreatitis has not been reported. Prior history of pancreatitis does not appear to be a risk factor for pancreatic inflammation in patients with COVID-19.
Complications | Timeframe | Likelihood
--- | --- | ---
autoimmune hemolytic anemia | variable | low

Warm or cold autoimmune hemolytic anemia (first episode) has been reported in 7 patients after the onset of COVID-19 symptoms and within the timeframe compatible with cytokine release syndrome. Four patients had indolent B lymphoid malignancy. It is unknown whether the hemolytic anemia is related to COVID-19 infection.[1070]

immune thrombocytopenia | variable | low

Immune thrombocytopenia has been reported rarely. The majority of cases were in patients >50 years of age, with only 7% of cases reported in children. The majority of cases were in patients with moderate to severe COVID-19; however, 7% of cases were in asymptomatic COVID-19 patients. Onset occurred in 20% of cases 3 weeks after the onset of COVID-19 symptoms, with most cases reported after clinical recovery. Severe life-threatening bleeding was uncommon. Treatment involved the use of corticosteroids, intravenous immune globulin, and thrombopoietin-receptor agonists.[1071]

subacute thyroiditis | variable | low

Cases of subacute thyroiditis have been reported in patients with COVID-19 who require intensive care.[1072] The first known case of subacute thyroiditis was reported in an 18-year-old woman. Subacute thyroiditis is a thyroid disease of viral or post-viral origin.[1073]

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.[1074] 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.[1075]

Prognosis

Mortality

The leading cause of death is respiratory failure from acute respiratory distress syndrome (ARDS).[882] The overall pooled mortality rate from ARDS in COVID-19 patients is 39%; however, this varies significantly between countries (e.g., China 69%, Iran 28%, France 19%, Germany 13%).[883] 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.[884]

People <65 years of age have a very small risk of death even in pandemic epicenters, and deaths in people <65 years of age without any underlying conditions is rare.[885]

Mortality rates have decreased over time despite stable patient characteristics. Mortality rates decreased sharply in the US over the first 6 months of the pandemic.[886] [887] In one study 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.[888] In another study in the UK, adjusted in-hospital mortality decreased from 52.2% in the first week of March 2020 to 16.8% in the last week of May 2020.[889] This may reflect the impact of changes in hospital strategy and clinical processes, and better adherence to
Follow up

Evidence-based standard of care therapies for critical illness over time, such as high-flow nasal oxygen to avert intubation, prone positioning, and decreased use of mechanical ventilation. Further studies are needed to confirm these results and investigate causal mechanisms.

Infection fatality rate (IFR)

- Defined as the proportion of deaths among all infected individuals including confirmed cases, undiagnosed cases (e.g., asymptomatic or mildly symptomatic cases), and unreported cases. The IFR gives a more accurate picture of the lethality of a disease compared with the case fatality rate.
- Approximately 10% of the global population may have been infected by October 2020, with an estimated overall IFR of 0.15% to 0.2% (0.03% to 0.04% in those <70 years of age).[890]
- The US Centers for Disease Control and Prevention's current best estimate of the IFR, according to age (as of 19 March 2021).[141]
  - 0 to 17 years – 0.002%
  - 18 to 49 years – 0.05%
  - 50 to 64 years – 0.6%
  - ≥65 years – 9%.
- Based on these figures, the overall IFR for people <65 years of age is approximately 0.2%.
- The IFR can vary across locations. A meta-analysis reports the point estimate of the IFR to be 0.68% across populations, with high heterogeneity (as of July 2020). The rate varied across locations from 0.17% to 1.7%.[891]
- Among people on board the Diamond Princess cruise ship, a unique situation where an accurate assessment of the IFR in a quarantined population can be made, the IFR was 0.85%. However, all deaths occurred in patients >70 years of age, and the rate in a younger, healthier population would be much lower.[892]
- These estimates have limitations and are likely to change as more data emerge over the course of the pandemic.

Seroprevalence studies

- Estimates of the IFR can be inferred from seroprevalence studies.
  - Worldwide seroprevalence estimates vary. Seroprevalence in the general population has been estimated to be approximately 8%, with higher rates reported in close contacts (18%) and high-risk healthcare workers (17.1%). Pooled estimates of seroprevalence in the general population were highest in the South-East Asian (19.6%), African (16.3%), and Eastern Mediterranean (13.4%) regions. Lower estimates were reported in the Americas (6.8%), European (4.7%), and Western Pacific (1.7%) regions.[893]
  - Current seroprevalence estimates for 10 sites in the US are available. [CDC: commercial laboratory seroprevalence survey data] (https://covid.cdc.gov/covid-data-tracker/#serology-surveillance)
  - These studies suggest that the prevalence of infections is much higher than the official case counts suggest, and therefore the virus is much less lethal than initially thought.

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/hospitalised cases are likely to be tested.
- The World Health Organization’s current estimate of the global CFR is 2.2% (as of 21 March 2021).[894] 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%.[49]
- CFR varies considerably between countries.
Follow up

- In China, the overall CFR has been reported to be between 1.4% and 2.3% (0.9% in patients without comorbidities).[4] [895]

- CFR increases with age.

- In China, the majority of deaths were in patients ages ≥60 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%).[7]
- In China, the majority of deaths were in patients ages ≥60 years.[4] 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%).[895]
- 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%).[896]
- Deaths are rare in children.[7] [21] 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.[897]

- 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).[4]

- CFR increases with disease severity.

- The CFR is highest in patients with critical disease, ranging from 26% to 67% in studies.[4] [898] [899]

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.[900]
- There is currently no set case definition of a confirmed case, and case definitions vary. A positive polymerase chain reaction (PCR) result is sometimes the only criterion for a case to be recognized; however, a positive PCR test does not necessarily equal a diagnosis of COVID-19, or mean that a person is infected or infectious.[901] [902]
- The number of deaths reported on a particular day may not accurately reflect the number of deaths from the previous day due to delays associated with reporting deaths. This makes it difficult to know whether deaths are falling over time in the short term.[903]
- Patients who die "with" COVID-19 and patients who die "from" COVID-19 may be counted towards the death toll in some countries. For example, in Italy only 12% of death certificates reported direct causality from COVID-19, while 88% of patients who died had at least one comorbidity.[900] [904]

Mortality rate by country

- The number of deaths (per 100,000 population) for different countries varies:[905]
  - South Korea – 0.7
  - Japan – 1.2
  - Australia – 3.3
  - Germany – 11.3
  - Canada – 24.6
  - France – 46.6
  - Sweden – 57.4
  - Italy – 59.1
  - US – 60.3
Coronavirus disease 2019 (COVID-19)

Follow up

- UK – 62.6
- Spain – 65.0
- Belgium – 86.8.

Prognostic factors

Prognostic factors that have been associated with increased risk of severe disease and mortality include:[758] [906] [907]

- Patient factors
  - Increasing age
  - Male sex
  - Obesity
  - Smoking history
  - Blood type A
  - Frailty
- Presence of comorbidities
  - Hypertension
  - Cardiovascular disease
  - Heart failure
  - Cerebrovascular disease
  - Dementia
  - Diabetes
  - Chronic lung disease
  - COPD
  - Active malignancy
  - Immunosuppression
  - Chronic kidney disease
- Symptoms/signs
  - Myalgia
  - Sputum production
  - Chills
  - Nausea
  - Dyspnea
  - Tachypnea
  - Hypoxemia
  - Respiratory failure
  - Hypotension
  - Tachycardia
- Investigations
  - Lymphopenia
  - Leukocytosis
  - Neutrophilia
Coronavirus disease 2019 (COVID-19) Follow up

• Thrombocytopenia
• Hypoalbuminemia
• Liver, kidney impairment, or cardiac injury
• Elevated inflammatory markers (C-reactive protein, procalcitonin, erythrocyte sedimentation rate)
• Elevated lactate dehydrogenase
• Elevated creatine kinase
• Elevated cardiac markers
• Elevated D-dimer
• Elevated interleukin-6
• 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.[908]

A ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) ≤200 mmHg and respiratory failure at admission are also independently associated with an increased risk of in-hospital mortality.[909] Almost half of patients who received invasive mechanical ventilation died. The mortality rate was higher in older patients >80 years (84%) compared with younger patients ≤40 years (48%).[910]

Hospital readmission

Approximately 9% of over 106,000 patients were readmitted to the same hospital within 2 months of discharge from the initial hospitalization. Multiple readmissions occurred in 1.6% of patients. The median time from discharge to the first readmission was 8 days. Less than 0.1% of patients died during readmission. Risk factors for readmission include:[911]

• Age ≥65 years
• Presence of chronic conditions (COPD, heart failure, diabetes, chronic kidney disease, obesity)
• Hospitalization within the 3 months preceding the first COVID-19 hospitalization
• Discharge to a skilled nursing facility or with home health care.

Reinfection

Reinfection refers to a new infection following previous confirmed infection (i.e., severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] real-time reverse transcription polymerase chain reaction [RT-PCR] positive), and is distinct from persistent infection and relapse. There is currently no standard case definition for SARS-CoV-2 reinfection.[646]

There is limited information about reinfection.

• Recurrent RT-PCR positivity in patients 1 to 60 days after recovery ranges between 7% to 23% in studies, with an estimated pooled rate of 12%.[912] Patients with longer initial illness and younger age were more likely to experience recurrent RT-PCR positivity, while those with severe disease, diabetes, and a low lymphocyte count were less likely.[913] It is currently unclear whether this is due to reinfection; whether it is due to factors such as the type of specimen collection and technical errors associated with swab testing, infection by mutated SARS-CoV-2, or persistent viral shedding; or whether the test result was a false-negative at the time of discharge.[914]
• Studies have repeatedly reported positive RT-PCR tests for up to 90 days after initial infection; therefore, it is most likely that these cases are actually protracted initial infections. It is important to note that although persistent viral shedding has been reported for up to 90 days after the onset of infection, replication-competent virus has not been identified 10 to 20 days after the onset of symptoms (depending on disease severity).[915] A cohort study of 200 patients with past infection found that despite persistent pharyngeal RT-PCR positivity for up to 90 days after recovery, transmission to close
coronavirus disease 2019 (COVID-19)

Follow up

contacts was not observed, indicating that these patients are not contagious at the post-symptomatic stage of infection.[916]

Cases of reinfection are rare.

- Cases of possible reinfection have been reported in many countries including Hong Kong, India, Ecuador, the US, and Belgium.[917] [918] [919] [920] [921] [922]
- Cases of reinfection with SARS-CoV-2 variants have been reported in Brazil, the UK, and South Africa.[923] [924] [925] [926]

Consider reinfection in the following circumstances:[646]

- 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.[646]

Management

- Manage patients with suspected reinfection as if they are infectious, as for a new or first infection. Advise the patient to self-isolate pending further investigation and clinical risk assessment. It is important to note that illness due to reinfection may not necessarily follow the same clinical course as the previous episode.[646]

Immunology

The immune response to SARS-CoV-2 is not yet fully understood, but involves both cell-mediated and antibody-mediated immunity. This is an area of rapidly emerging new evidence.

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.[927]

Antibody-mediated immunity

- Current evidence is uncertain to predict the presence, level, or durability of natural immunity conferred by SARS-CoV-2 antibodies against reinfection.[928]
- 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.[929]
- Maternal IgG antibodies to SARS-CoV-2 have been found to transfer across the placenta after infection in pregnant women.[930]
• There were some early studies that suggested asymptomatic people may have a weaker antibody response to infection; however, this has not been confirmed.[931]
• Antibodies have been detected up to 8 months after infection.[932]

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.[933]
• 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.[934] [935]
• Emerging data suggest that T-cell responses are largely unaffected by SARS-CoV-2 variants.[936]

Evidence suggests that infection with SARS-CoV-2 is likely to confer protective immunity against reinfection.[937] [938] [939] [940]

• A Public Health England study found that naturally acquired immunity, as a result of past infection, provides 83% protection against reinfection compared with people who have not had the disease previously, and protection appeared to last for at least 5 months.[941]
• Similarly, a population-level observational study among 4 million PCR-tested people in Denmark found protection against repeat infection in the population to be 80% or higher in those younger than 65 years of age, and 47% in those older than 65 years of age. There was no evidence of waning protection over time.[942]
• According to a large, retrospective study, people who were seropositive for SARS-CoV-2 appeared to be at lower risk for future infection, for at least several months.[943]
• A study in over 12,000 healthcare workers found that prior SARS-CoV-2 infection that generated antibody responses offered protection from reinfection for most people in the 6 months following infection.[944]

Preexisting immunity to SARS-CoV-2

• Testing of blood samples taken before the COVID-19 pandemic has shown that some people already have immune cells that recognize SARS-CoV-2. Studies have reported T-cell reactivity against SARS-CoV-2 in 20% to 50% of people with no known exposure to the virus.[945] Approximately 5% of uninfected adults and 62% of uninfected children aged 6 to 16 years had antibodies that recognize SARS-CoV-2 in one study.[946]
• This may be a consequence of true immune memory derived in part from previous infection with common cold coronaviruses, or from other unknown animal coronaviruses. However, further research into whether there is preexisting immunity to SARS-CoV-2 in the human population is required.
Diagnostic guidelines

International


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## Treatment guidelines

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**Last published:** 2021

**COVID-19: guidance for health professionals**
[https://www.gov.uk/government/collections/wuhan-novel-coronavirus]  [645]

**Published by:** Public Health England  
**Last published:** 2021

**COVID-19: the green book, chapter 14a**

**Published by:** Public Health England  
**Last published:** 2021

**COVID-19: investigation and management of suspected SARS-CoV-2 reinfections**

**Published by:** Public Health England  
**Last published:** 2021
International

Published by: European Centre for Disease Prevention and Control  Last published: 2021

Published by: Royal College of Obstetricians and Gynaecologists (UK)  Last published: 2021

Published by: British Thoracic Society  Last published: 2021

Published by: Ministry of Health Singapore  Last published: 2021

Coronavirus disease (http://www.chinacdc.cn/jkzt/crb/zl/szkb_11803/) [872]
Published by: Chinese Center for Disease Control and Prevention  Last published: 2021

Published by: National Institute of Infectious Diseases Japan  Last published: 2021

COVID-19 infection (https://www.kansensho.or.jp/modules/topics/index.php?content_id=31) [874]
Published by: Japanese Association for Infectious Diseases  Last published: 2021

Published by: Department of Health Australia  Last published: 2021

Coronavirus specialty guides (https://www.nice.org.uk/covid-19/specialty-guides) [876]
Published by: NHS England  Last published: 2020

COVID-19 rapid guideline: managing the long-term effects of COVID-19 (https://www.nice.org.uk/guidance/ng188) [877]
Published by: National Institute for Health and Care Excellence (UK)  Last published: 2020

Published by: Scottish Intercollegiate Guidelines Network  Last published: 2020
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<tr>
<td><strong>Published by:</strong> Royal College of General Practitioners; Association for Palliative Medicine <strong>Last published:</strong> 2020</td>
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<td><strong>Published by:</strong> Chinese expert working panel <strong>Last published:</strong> 2020</td>
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<td><strong>Published by:</strong> First Affiliated Hospital, Zhejiang University School of Medicine <strong>Last published:</strong> 2020</td>
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<tr>
<td><strong>Published by:</strong> National Health Commission of the People's Republic of China; National Administration of Traditional Chinese Medicine of the People's Republic of China <strong>Last published:</strong> 2020</td>
</tr>
<tr>
<td><strong>Published by:</strong> Peking Union Medical College Hospital <strong>Last published:</strong> 2020</td>
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</table>
## Online resources


4. BMJ talk medicine: the BMJ podcast ([https://www.bmj.com/archive/podcasts](https://www.bmj.com/archive/podcasts)) (external link)

5. BMJ Best Practice: Management of coexisting conditions in the context of COVID-19 ([https://bestpractice.bmj.com/topics/en-us/3000190#important-update](https://bestpractice.bmj.com/topics/en-us/3000190#important-update)) (external link)


11. COG-UK: data ([https://www.cogconsortium.uk/](https://www.cogconsortium.uk/)) (external link)


20. BMJ: covid-19 – a remote assessment in primary care (https://www.bmj.com/content/368/bmj.m1182) (external link)


24. BMJ: facemasks for the prevention of infection in healthcare and community settings (https://www.bmj.com/content/350/bmj.h694) (external link)


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

30. BMJ Practice Pointer: interpreting a covid-19 tests result (https://www.bmj.com/content/369/bmj.m1808) (external link)
<table>
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<tr>
<th>No.</th>
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<tr>
<td>31.</td>
<td>BMJ practice pointer: testing for SARS-CoV-2 antibodies (<a href="https://www.bmj.com/content/370/bmj.m3325">https://www.bmj.com/content/370/bmj.m3325</a>) (external link)</td>
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<td>42.</td>
<td>Clinical Frailty Scale (<a href="https://www.scfn.org.uk/clinical-frailty-scale">https://www.scfn.org.uk/clinical-frailty-scale</a>) (external link)</td>
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<td>44.</td>
<td>BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19 (<a href="https://www.bmj.com/content/370/bmj.m3379">https://www.bmj.com/content/370/bmj.m3379</a>) (external link)</td>
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46. RECOVERY trial (https://www.recoverytrial.net/) (external link)
50. BMJ webinar: long COVID – how to define it and how to manage it (https://www.bmj.com/content/370/bmj.m3489) (external link)
51. BMJ: management of post-acute covid-19 in primary care (https://www.bmj.com/content/370/bmj.m3026) (external link)
52. The BMJ 10-minute consultation: what is my covid risk? (https://www.bmj.com/content/372/bmj.n637) (external link)
56. Health Education England: adult pulse oximetry monitoring video (https://www.youtube.com/watch?v=ifnYjD4IKus&t=141s) (external link)
59. NaTHNac: travel health pro (https://travelhealthpro.org.uk/) (external link)
<table>
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<th></th>
<th>Online resources</th>
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<tr>
<td>61.</td>
<td>UK Department for Transport (<a href="https://www.gov.uk/government/organisations/department-for-transport">https://www.gov.uk/government/organisations/department-for-transport</a>) (external link)</td>
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</tbody>
</table>
**Key articles**

**References**


44. Kissler S, Fauver JR, Mack C, et al. Densely sampled viral trajectories suggest longer duration of acute infection with B.1.1.7 variant relative to non-B.1.1.7 SARS-CoV-2. 2021 [internet publication]. Full text (https://dash.harvard.edu/handle/1/37366884)


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348. Doshi P. Pandemrix vaccine: why was the public not told of early warning signs? BMJ. 2018 Sep 20;362:k3948.


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<th>Reference</th>
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Full text (https://www.journalofinfection.com/article/S0163-4453(20)30099-2/fulltext)  

Full text (https://www.ejradiology.com/article/S0720-048X(20)30150-9/pdf)  

Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7804384/)  

Full text (https://www.birpublications.org/doi/10.1259/bjr.20201039)  


Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7657023/)  

Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7549426/)  

Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7108162/)  


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823. Mesoblast Limited. Mesoblast update on COVID-19 ARDS trial. 2020 [internet publication]. Full text (http://investorsmedia.mesoblast.com/static-files/bc0ce366-1c50-46ce-a9d4-d06b7ce403e5)


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881. National Health Commission of the People’s Republic of China; National Administration of Traditional Chinese Medicine of the People’s Republic of China. Diagnosis and
Coronavirus disease 2019 (COVID-19) References


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Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7194613/)  

Full text (https://www.bmj.com/content/368/bmj.m1091.long)  


Full text (https://www.jci.org/articles/view/137647/pdf)  

Full text (https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30404-5/fulltext)  

Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7228732/)  

Full text (https://www.jpeds.com/article/S0022-3476(20)30985-9/fulltext)  

Full text (https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e2.htm)  

Full text (https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30651-4/fulltext)  
Coronavirus disease 2019 (COVID-19)

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Figure 1: Number of COVID-19 cases reported weekly by WHO Region, and global deaths, as of 21 March 2021

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: Virus replication cycle

BMJ. 2020;371:m3862
<table>
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<tr>
<th>mRNA vaccines</th>
<th>Pfizer/BioNTech</th>
<th>Moderna</th>
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<tbody>
<tr>
<td><strong>Vaccine type</strong></td>
<td>Lipid nanoparticle-formulated mRNA vaccine that encodes the SARS-CoV-2 spike protein</td>
<td></td>
</tr>
<tr>
<td><strong>Overall efficacy</strong></td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≥16 years of age</td>
<td>≥18 years of age</td>
</tr>
<tr>
<td><strong>Authorized dose</strong></td>
<td>TWO-DOSE REGIMEN  0.3 mL (30 mcg) IM; second dose at least 21 days after</td>
<td>TWO-DOSE REGIMEN  0.5 mL (100 mcg) IM; second dose at least 28 days after</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Hypersensitivity to active substance or any excipients; immediate allergic reaction to first dose (should not get second dose)</td>
<td></td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
<td>History of anaphylaxis/allergic reactions</td>
<td></td>
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<tr>
<td></td>
<td>Acute severe febrile illness</td>
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<tr>
<td></td>
<td>Bleeding disorders or anticoagulation</td>
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<tr>
<td></td>
<td>Immune-compromised</td>
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<tr>
<td></td>
<td>Pregnancy and breastfeeding</td>
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<tr>
<td></td>
<td>Previous treatment with COVID-19 monoclonal antibodies/plasma</td>
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<tr>
<td><strong>Adverse events</strong></td>
<td>Common: headache; arthralgia; myalgia; injection-site reactions; fatigue; fever; chill; nausea; vomiting; diarrhea; rash; lymphadenopathy</td>
<td>Uncommon: malaise; acute peripheral facial paralysis; anaphylaxis; hypersensitivity; face swelling (if dermatologic fillers present)</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>Interactions with other vaccines/drugs have not been studied (WHO recommends at least 14 days between COVID-19 vaccines and others)</td>
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Figure 4: Comparison of selected authorized mRNA COVID-19 vaccines. Data is evolving; consult local drug formulary or guidelines for detailed information for your location. *Data based on phase 3 clinical trials - see Vaccine efficacy clinical trial data and Vaccine safety clinical trial data sections below for detailed information. **Dose schedules may differ in some locations. Last reviewed/updated: 24 March 2021#
Figure 5: Comparison of selected authorized viral vector COVID-19 vaccines. Data is evolving; consult local drug formulary or guidelines for detailed information for your location. *Data based on phase 3 clinical trials - see Vaccine efficacy clinical trial data and Vaccine safety clinical trial data sections below for detailed information. **Dose schedules may differ in some locations. Last reviewed/updated: 24 March 2021

BMJ Best Practice editorial team; compiled using data from the US product information
Figure 6: 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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Please note that recommended formulations and doses may differ between drug databases, drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

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Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example, 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

**Figure 1 – BMJ Best Practice Numeral Style**
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