BMJ Best Practice

# Coronavirus disease 2019 (COVID-19)

The right clinical information, right where it's needed

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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 aetiology 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, and dyspnoea, although some patients may be asymptomatic. Complications of severe disease include, but are not limited to, multi-organ failure, septic shock, and blood clots.

# Epidemiology

Adults

- In China, 87% of confirmed cases were aged 30 to 79 years and 3% were aged 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 hospitalised patients.[6]
- In the US, older patients (aged ≥65 years) accounted for 31% of all cases, 45% of hospitalisations, 53% of intensive care unit admissions, and 80% of deaths, with the highest incidence of severe outcomes in patients aged ≥85 years.[7]

Children

- Children are less likely to be affected than adults, and account for up to 9% of confirmed cases depending on geographical location:[4] [8] [9] [10] [11] [12] [13]
    - 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)
    - UK: <5% (increased risk in males)
    - US: 9.1% (or 501 cases per 100,000 children in the population) as of 6 August.
    - [American Academy of Pediatrics: children and COVID-19 – state-level data report]
- Most cases are from familial clusters, or children who have a history of close contact with an infected patient.[14] It appears that children generally don't spread the virus to household contacts.[15] Unlike adults, children do not seem to be at higher risk for severe illness based on age or sex.[16]

Pregnant women

- In the UK, the estimated incidence of admission to hospital with confirmed severe acute respiratory syndrome coronavirus 2 (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 aged 35 years or older, 56% were from Black or other ethnic minority groups, 69% were overweight or obese, and 34% had pre-existing comorbidities.[17]
- In the US, according to an analysis of 8200 infected pregnant women, Hispanic and non-Hispanic Black pregnant women appear to be disproportionately affected during pregnancy.[18]

Healthcare workers



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- Infection rates in healthcare workers vary. A meta-analysis found that the overall proportion of healthcare workers who tested positive for SARS-CoV-2 among all patients with COVID-19 was 10.1%. This proportion varied according to location: 4.2% in China; 17.8% in the US; and 9% in Italy. 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.[19] In the UK, 14% to 44% of healthcare workers who were screened had evidence of infection detected by molecular or serological testing.[20] [21] Around 10% of all COVID-19 infections in England between 26 April and 7 June were among patient-facing healthcare workers and social care workers.[22] In the Netherlands, 6% of healthcare workers who were tested were positive for SARS-CoV-2.[23] The prevalence of SARS-CoV-2 antibodies in a large cohort study of healthcare workers in New York was 13.7%; however, only 56% of the invited sample of healthcare workers participated in the study.[24]
- 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.[25]

Current case counts

- [WHO: coronavirus disease (COVID-19) emergency dashboard]
- [WHO: coronavirus disease (COVID-2019) weekly epidemiological updates]
- [CDC: coronavirus disease 2019 (COVID-19) – cases in the US]
- [CDC: COVIDView]

# Aetiology

Virology

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown betacoronavirus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019.[26]
- Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), and others that circulate among mammals and birds. Rarely, animal coronaviruses can spread to humans and subsequently spread between people, as was the case with SARS and MERS.
- SARS-CoV-2 belongs to the *Sarbecovirus* subgenus of the *Coronaviridae* family, and is the seventh coronavirus known to infect humans. The virus has been found to be similar to SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV.[27] [28] The full genome has been determined and published in GenBank. [GenBank]
- A preliminary study suggests that there are two major types (or strains) of the SARS-CoV-2 virus in China, designated L and S. The L type was found to be more prevalent during the early stages of the outbreak in Wuhan City and may be more aggressive (although this is speculative), but its frequency decreased after early January. The relevance of this finding is unknown at this stage and further research is required.[29] Patients in Singapore infected with a SARS-CoV-2 variant with a 382-nucleotide deletion appeared to have a milder course compared with those infected with a wild-type virus.[30]

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[Fig-1]

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.[31] [32] [33]
- While the potential animal reservoir and intermediary host(s) are unknown at this point, studies suggest they may derive from a recombinant virus between the bat coronavirus and an origin-unknown coronavirus; however, this is yet to be confirmed.[27] [28] [34] [35] Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses.[36] [37] Over 5 months after the initial outbreak, the virus is yet to be identified in an animal host.[38]

Transmission dynamics

- 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 Huanan South China Seafood Market, whereas only 8.6% of cases after this date were linked to the market. This confirms that person-to-person spread occurred among close contacts since the middle of December 2019, including infections in healthcare workers.[33]
- 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. Transmission via fomites also appears to be likely. Airborne transmission can occur in healthcare settings during aerosol-generating procedures. There are some outbreak reports that suggest aerosol transmission is possible in the community; however, these reports relate to indoor crowded spaces with poor ventilation (e.g., restaurants, choir practice, fitness classes), and a detailed investigation of these clusters suggests that droplet and fomite transmission could also explain the transmission in these reports. Further research is required.[39]
- Preliminary reports suggested that the reproductive number ($R_0$), the number of people who acquire the infection from an infected person, was estimated to be 2.2 to 3.3.[33] [40] However, the $R_0$ may actually be lower in light of social distancing measures that have been instituted.[41]
- 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).[42] In healthcare settings, the virus is widely distributed in the air and on object surfaces (e.g., floors, rubbish bins, sickbed handrails, and computer mice) in both general wards and intensive care units, with a greater risk of contamination in the intensive care unit.[43] While viral RNA has been detected on surfaces and air samples across a range of acute healthcare settings, no virus has been cultured from these samples indicating that the deposition may reflect non-viable viral RNA.[44]
- The virus has been detected in faeces. The pooled detection rate of faecal SARS-CoV-2 RNA in patients with COVID-19 is approximately 44%. The rate is higher in female patients, those with gastrointestinal symptoms, and patients with severe disease.[45] Observational and mechanistic evidence supports the hypothesis that SARS-CoV-2 can infect and be shed from the gastrointestinal tract.[46] While faecal-oral transmission (or respiratory transmission through aerosolised faeces) may be possible, it has not been reported as yet.
- The contribution to transmission by the presence of the virus in other body fluids is unknown; however, the virus has been detected in blood, cerebrospinal fluid, pericardial fluid, pleural fluid, placental tissue, urine, semen, saliva, tears, and conjunctival secretions.[47] [48] [49] [50] [51] [52] [53] [54] [55] The



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presence of virus or viral components in these fluids or viral RNA shedding does not necessarily equate with infectivity. Sexually transmitted infection has not yet been reported.[54] The SARS-CoV-2 virus has been detected in the middle ear and mastoid in a small number of patients.[56]

- Nosocomial transmission in healthcare workers and patients has been reported in 44% of patients.[57] The nosocomial infection rate in a major London teaching hospital was around 15% during the peak of the outbreak, with a case fatality rate of 36% for this cohort.[58] Recent reports of healthcare workers exposed to index cases (not in the presence of aerosol-generating procedures) found no nosocomial transmission when contact and droplet precautions were used.[39]
- Widespread transmission has been reported in long-term care facilities, homeless shelters, and prisons, and on cruise ships (19% of 3700 passengers and crew were infected aboard the Diamond Princess).[59] [60] [61] [62] [63] A high rate of transmission has been reported in meat and poultry processing facility workers, likely due to the working environment (e.g., low temperatures, metallic surfaces) and a close working environment.[64] Several outbreaks have been reported.[65] [66] [67] [68] There is a lack of evidence for transmission in the school setting.[69]
- Clusters of cases originating from family gatherings, overnight youth camps, weddings, choir practices, fitness classes, religious gatherings, and churches have been reported.[70] [71] [72] [73] [74] [75] [76] Non-pharmaceutical interventions (e.g., arrival quarantine, social distancing, cloth face coverings, rapid isolation) may limit the incidence and spread in congregate settings according to a study at a US air force base.[77]
- The secondary attack rate among all close contacts is approximately 0.45% to 3.7%. The secondary attack rate among household members is higher and ranges from 4.6% to 30%.[78] [79] [80] [81] [82] The secondary attack rate is higher for spouse contacts of the index case. The rate lowered to 0% in one study where index patients were quarantined by themselves from the onset of symptoms.[81] The secondary attack rate in children is lower compared with adults. In one study, the secondary attack rate in children was 6.1%; children aged <5 years had lower rates of infection (1.3%) compared with older children following exposure to an infected household member. The risk of secondary infection in children was higher if the household index case was the mother.[83] The secondary attack rate in children exposed to a positive case in a childcare setting or school was 1.2% in one study.[84] 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).[82]

Symptomatic transmission

- Transmission mainly occurs from symptomatic people to others by close contact through respiratory droplets, by direct contact with infected people, or by contact with contaminated objects and surfaces.[2]

Presymptomatic transmission

- The incubation period is estimated to be between 1 and 14 days, with a median of 5 to 6 days. Some patients may be contagious during the incubation period, usually 1 to 3 days before symptom onset. Presymptomatic transmission still requires the virus to be spread by infectious droplets or by direct or indirect contact with bodily fluids from an infected person.[2] [85]
- Presymptomatic transmission has been reported in 12.6% of cases in China.[86] A study in Singapore identified 6.4% of patients among seven clusters of cases in which presymptomatic transmission was likely to have occurred 1 to 3 days before symptom onset.[87]
- The overall secondary attack rate for close contacts of presymptomatic people is approximately 3.3%, with a rate of 16.1% for household contacts, 1.1% for social contacts, and 0% for work contacts.[88]

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Asymptomatic transmission

- An asymptomatic case is a laboratory-confirmed case who does not develop symptoms. Transmission from an asymptomatic case is very unlikely. There is some evidence that spread from asymptomatic carriers is possible, although it is thought that transmission is greatest when people are symptomatic (especially around the time of symptom onset).[89] [90] [91] [92] [93] [94] [95] According to the World Health Organization (WHO), asymptomatic individuals are much less likely to transmit the virus than those who develop symptoms.[96] A case of an asymptomatic patient with 455 contacts found that none of the contacts (which included other patients, family members, and healthcare workers) became infected.[97] The majority of asymptomatically infected people remained asymptomatic throughout the course of infection in one cohort study.[98] Another small retrospective cohort study found no evidence of asymptomatic transmission from nine carriers to any close contacts over an average of 85 days.[99] The secondary attack rate for asymptomatic people was 0.3% in one study of 3410 close contacts of 391 index cases. This supports the view of the WHO that asymptomatic cases were not the major drivers of the overall epidemic dynamics.[82] Despite the reassuring data, there is some limited evidence for suspected asymptomatic transmission.[100]
- Estimating the prevalence of asymptomatic cases in the population is difficult. A meta-analysis of over 50,000 patients found that approximately 15.6% of confirmed COVID-19 patients are asymptomatic, and nearly half of these patients will develop symptoms later. Children are more likely to have asymptomatic infection.[101] Studies with a large sample size (>1000) estimate that 1.2% to 12.9% of people who contract COVID-19 are likely to be asymptomatic.[102] The best evidence so far comes from the Diamond Princess cruise ship, which was quarantined with all passengers and crew members repeatedly tested and closely monitored. A modelling study found that approximately 700 people with confirmed infection (18%) were asymptomatic.[103] However, a Japanese study of citizens evacuated from Wuhan City estimates the rate to be closer to 31%.[104] Early data from an isolated village of 3000 people in Italy estimates the figure to be higher at 50% to 75%.[105] Other studies ranged from 4% to 80%.[106] A narrative review of 16 cohorts found that the asymptomatic infection rate could be as high as 40% to 45%.[107]
- Data from a long-term care facility in the US found that 30% of patients with positive test results were asymptomatic (or presymptomatic) on the day of testing.[108] In a skilled nursing facility, 64% of residents tested positive 3 days after one resident tested positive; 56% of the residents who tested positive and participated in point-prevalence surveys were asymptomatic at the time of testing, although most went on to develop symptoms.[109]
- Asymptomatic transmission from healthcare workers may be a source of transmission. Among 249 healthcare workers who worked in hospital units with COVID-19 patients for 1 month, 7.6% tested positive for SARS-CoV-2 antibodies; however, only 58% of those with positive serology reported symptoms of a prior viral illness.[110] 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.[111]
- Asymptomatic (or paucisymptomatic) transmission has been reported in family clusters.[112]
- The proportion of asymptomatic cases in children is thought to be significant, and children may play a role in community spread.[113] The pooled proportion of asymptomatic infection in children has been estimated to be around 40%.[114] However, there is a case report of an asymptomatic child who did not transmit the disease to 172 close contacts, despite close interactions within schools. This suggests that there may be different transmission dynamics in children.[115]

Superspreading events



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- Multiple superspreading events have been reported with COVID-19. These events are associated with explosive growth early in an outbreak and sustained transmission in later stages.[116]
- Superspreaders can pass the infection on to large numbers of contacts, including healthcare workers. This phenomenon is well documented for infections such as severe acute respiratory syndrome (SARS), Ebola virus infection, and MERS.[117] [118]
- Some of these individuals are also supershedders of virus, but the reasons underlying superspreader events are often more complex than just excess virus shedding and can include a variety of behavioural and environmental factors.[117]

Perinatal transmission

- Vertical transmission is possible but appears to occur in a minority of cases (3.2%) in the third trimester.[119] Suspected intrauterine transmission and transplacental transmission have been reported.[120] [121] The rate of infection is not greater when the baby is born vaginally, breastfed, or allowed contact with the mother.[122]
- Viral fragments have been detected in breast milk, but the significance of this is unknown.[123] [124] [125] A study in 18 women with COVID-19 who were breastfeeding found that while reverse-transcription polymerase chain reaction (RT-PCR) detected SARS-CoV-2 RNA in one sample, culture to detect replication-competent virus was negative. This suggests that transmission via breast milk is unlikely.[126]
- Perinatal transmission is unlikely to occur if correct hygiene precautions are taken. In a study of 1481 deliveries, 8% of mothers tested positive for SARS-CoV-2. About 83% of neonates roomed in with their mother and were breastfed. All neonates who were tested with reverse-transcription polymerase chain reaction (RT-PCR) at 5 to 7 days and 14 days of life tested negative for SARS-CoV-2.[127]

Viral load and shedding

- High viral loads have been detected in nasal and throat swabs soon after symptom onset, and it is thought that the viral shedding pattern may be similar to that of patients with influenza. An asymptomatic patient was found to have a similar viral load compared with symptomatic patients.[128] [129] High viral load at baseline may be associated with more severe disease and risk of disease progression.[130]
- Pharyngeal viral shedding is high during the first week of symptoms when symptoms are mild or prodromal, peaking on day 4. This suggests active virus replication in upper respiratory tract tissues.[131]
- The median duration of viral shedding has been estimated to be between 8 and 20 days after symptoms resolve. However, the virus has been detected for up to 60 days in various samples, and for 104 days in one pregnant woman.[132] [133] [134] [135] [136] [137] [138] Viral shedding continued until death in non-survivors.[132]
- Duration of viral shedding was longer in symptomatic patients compared with asymptomatic patients (25.2 days versus 22.6 days).[139] The median duration of shedding was lower in mild illness compared with severe illness (14 days versus 21 days).[140]
- Viral shedding in stool has been detected in 41% of patients.[141] The duration of viral shedding is significantly longer in stool samples than in respiratory and serum samples. The median duration of viral shedding in stool samples was 22 days, compared with 18 days in respiratory samples and 16 days in serum samples.[140]

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- 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.[142]
- There is no convincing evidence that duration of viral shedding correlates with duration of infectivity.[143]

# Pathophysiology

The pathophysiology of COVID-19 is not fully understood; however, it has been confirmed that SARS-CoV-2 binds to the angiotensin-converting enzyme-2 (ACE2) receptor in humans, which suggests a similar pathogenesis to SARS.[28] [144] 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.[145] 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.[146] [147]

Based on an analysis of single-cell RNA sequencing datasets derived from major human physiological systems, the organs considered more vulnerable to SARS-CoV-2 infection due to their ACE2 expression levels include the lungs, heart, oesophagus, kidneys, bladder, and ileum.[148] This may explain the extrapulmonary manifestations associated with infection. 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.[149]

The virus uses the host transmembrane protease serine 2 (TMPRSS2) for S protein priming and fusion of viral and host cell membranes.[150] A furin-like cleavage site has been identified in the spike protein of the virus; this does not exist in other SARS-like coronaviruses.[151]

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 generalised 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 haemorrhage, and vasculitis. Significant new blood vessel growth through intussusceptive angiogenesis distinguishes the pulmonary pathology of COVID-19 from severe influenza infection.[152] [153] [154] [155] [156] [157]

Histopathological 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.[158] The virus has also been frequently detected in the myocardium in autopsy studies.[159]

There is a hypothesis that COVID-19 is a disease of the endothelium.[160] [161] [162] Endotheliopathy and platelet activation appear to be important features of COVID-19 in hospitalised patients and are likely to be associated with coagulopathy, critical illness, and death.[163] 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.[164]


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Genetic factors are thought to play a role in the pathogenesis. 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.[165]

# Classification

## World Health Organization: COVID-19 disease severity[2]

Mild illness

- Symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia.
- Common symptoms include fever, cough, fatigue, anorexia, dyspnoea, and myalgia. Other non-specific symptoms include sore throat, nasal congestion, headache, diarrhoea, nausea/vomiting, and loss of smell/taste.
- Older people and immunosuppressed people may present with atypical symptoms (e.g., fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium, absence of fever).
- Symptoms due to physiological adaptations of pregnancy or adverse pregnancy events (e.g., dyspnoea, 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, dyspnoea, fast breathing) but no signs of severe pneumonia, including blood oxygen saturation levels ($SpO_2$) ≥90% on room air.
- Children: clinical signs of non-severe 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, dyspnoea, fast breathing) plus one of the following:
    - Respiratory rate >30 breaths/minute
    - Severe respiratory distress
    - $SpO_2$ <90% on room air.
- Children: clinical signs of pneumonia (i.e., cough or difficulty in breathing) plus at least one of the following:
    - Central cyanosis or $SpO_2$ <90%
    - Severe respiratory distress (e.g., fast breathing, grunting, very severe chest indrawing)
    - General danger sign

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- Inability to breastfeed or drink, lethargy or unconsciousness, or convulsions.

- While the diagnosis can be made on clinical grounds, chest imaging may assist in diagnosis and identify or exclude pulmonary complications.

Critical disease

- Presence of acute respiratory distress syndrome (ARDS), sepsis, or septic shock.
- Other complications include acute pulmonary embolism, acute coronary syndrome, acute stroke, and delirium.

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

Asymptomatic or presymptomatic infection

- People who test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) but have no symptoms.

Mild illness

- People who have any of various signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal imaging.

Moderate illness

- People who have evidence of lower respiratory disease by clinical assessment or imaging and an oxygen saturation ($SpO_2$) >93% on room air at sea level.

Severe illness

- People who have respiratory frequency >30 breaths per minute, $SpO_2$ ≤93% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($PaO_2/FiO_2$) <300, or lung infiltrates >50%.

Critical illness

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



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# Primary prevention

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 1 metre (3 feet) between patients.[303]
- Implement standard precautions at all times:[303]
    - 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:[303]
    - 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.[303]
    - Some countries and organisations 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.[303]
- 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on molecular and serological testing when they returned home, despite all participants having direct contact with COVID-19 patients and performing at least one aerosol-generating procedure.[304] 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.[305]
- Detailed infection prevention and control guidance is available:
    - [WHO: infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed]
    - [CDC: interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 (COVID-19) pandemic]
    - [BMJ: covid-19 – PPE guidance]

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.[306] Most patients can be managed remotely by telephone or video consultations. Algorithms for dealing with these patients are available:
    - [BMJ: covid-19 in primary care (UK)]
    - [BMJ: covid-19 – a remote assessment in primary care]

General prevention measures for the general public



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- People should be advised to:[307] [308]
    - Wash hands often with soap and water for at least 20 seconds or an alcohol-based hand sanitiser (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 1 metre [3 feet]) including shaking hands, particularly those who are sick, have a fever, or are coughing or sneezing. Avoid going to crowded places. It is important to note that recommended distances differ between countries (for example, 2 metres is recommended in the US and UK) and you should consult local guidance. However, there is no evidence to support a distance of 2 metres[309]
    - 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 (travellers 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]
- [WHO: coronavirus disease (COVID-19) advice for the public]
- [Centre for Evidence-Based Medicine: what is the evidence to support the 2-metre social distancing rule to reduce COVID-19 transmission?]

Face masks for the general public

- Recommendations on the use of face masks in community settings vary between countries.[310] 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 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.[96] [311] 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 lacking.[312]
- The World Health Organization (WHO) recommends that people with symptoms of COVID-19 should wear a medical mask, self-isolate, and seek medical advice as soon as possible. The WHO also now encourages the general public to wear medical or cloth masks in specific situations and settings (e.g., areas with known or suspected widespread transmission and limited or no capacity to implement other containment measures such as social distancing, contact tracing, and testing; settings where social distancing cannot be achieved, particularly in vulnerable populations). This recommendation is based on observational evidence only.[96]
- The Centers for Disease Control and Prevention (CDC) recommends that homemade cloth face coverings can be worn in public settings where social distancing measures are difficult to maintain (e.g., pharmacies, supermarkets), especially in areas where there is significant community transmission.[313]
- 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. It is important to wash your hands with soap and water (or an alcohol-based sanitiser) prior to putting on a face mask, and to remove it correctly. Used masks should be disposed of properly.[96]
- 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 non-medical masks


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are not changed when wet or soiled; headache and/or breathing difficulties; facial skin lesions, irritant dermatitis, or worsening acne; discomfort; difficulty communicating; false sense of security; poor compliance; waste management issues; and difficulties for patients with chronic respiratory conditions or breathing problems.[96] 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.[314]

- 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.[315] The filtration, fit, effectiveness, and performance of cloth masks are inferior to medical masks and respirators. Protection may be improved by selecting appropriate material, increasing the number of mask layers, and using masks with a design that provides filtration and fit.[316]

- [BMJ: facemasks for the prevention of infection in healthcare and community settings]
- [BMJ: analysis – face masks for the public during the covid-19 crisis]

Alcohol-based hand sanitisers

- The CDC has issued a warning about alcohol-based sanitisers containing methanol (which may be labelled 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 co-ordination, decreased level of consciousness) who report ingestion of hand sanitiser or frequent repeated topical use. Cases of permanent blindness and death have been reported.[317]
- Frequent use of hand sanitisers may result in antimicrobial resistance. Accidental ingestion, especially by children, has been reported.[318]

Screening and quarantine

- People travelling 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. Combined screening of airline passengers on exit from an affected area and on arrival elsewhere has been relatively ineffective when used for other infections such as Ebola virus infection, and has been modelled to miss up to 50% of cases of COVID-19, particularly those with no symptoms during the incubation period.[319] Symptom-based screening processes have been reported to be ineffective in detecting SARS-CoV-2 infection in a small number of patients who were later found to have evidence of SARS-CoV-2 in a throat swab.[320]

- Enforced quarantine is being used to isolate easily identifiable cohorts of people at potential risk of recent exposure (e.g., groups evacuated by aeroplane from affected areas, people returning to their home countries before border closures, or groups on cruise ships with infected people on board).[321] The psychosocial effects of enforced quarantine may have long-lasting repercussions.[322] [323] 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.[324]
- Travellers who arrive in the UK are required to self-isolate for 14 days. [Public Health England: coronavirus (COVID-19) – how to self-isolate when you travel to the UK]

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, non-essential business closures, bans on gatherings, school and university closures, travel restrictions and bans, remote working, quarantine of exposed people/travellers).
- 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.[325] [326]



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- 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.[327]
- [Public Health England: staying alert and safe (social distancing)]

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 minimising 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:[328]
    - 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., sickle cell anaemia, severe combined immunodeficiency)
    - People on immunosuppression therapies sufficient to significantly increase the risk of infection
    - 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 judgement and an assessment of their needs.
- The UK government recommended shielding for certain groups of people until 31 July, and paused shielding from 1 August. Shielding recommendations may be necessary again if community transmission begins to rise significantly. The easing of shielding restrictions does not apply to extremely vulnerable people living in areas that are under local lockdown.[328] Consult current guidance for specific recommendations (recommendations may differ between countries).
    - [Public Health England: guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19]
- Shielding advice for children and young adults is available. Shielding of clinically extremely vulnerable children and young people is not currently recommended in the UK. Consult current guidance for specific recommendations (recommendations may differ between countries).
    - [Public Health England: guidance for young people on shielding and protecting people most likely to become unwell if they catch coronavirus]
    - [Royal College of Paediatrics and Child Health: COVID-19 – 'shielding' guidance for children and young people]

Vaccines

- Vaccines are in development, but it may take at least 12 to 18 months before one is available. According to news reports, a vaccine has been approved in Russia; however, it appears to have not completed large-scale clinical trials including phase 3 trials.[329] Several vaccine candidates are currently approved for human testing through clinical trials, including mRNA and DNA platform vaccines, adenovirus vector vaccines, and inactivated virus vaccines.[330]
- Previous trials of coronavirus vaccines identified cellular immunopathology and antibody-dependent enhancement (ADE) as potential safety issues, so there are concerns over ADE of SARS-CoV-2 due to prior exposure to other coronaviruses (such as those that cause the common cold).[331] [332]
- Results from preliminary animal and human studies are now available, but scientists urge caution over the results.[333]
- Ad5-nCoV: a recombinant adenovirus type-5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike glycoprotein. Results from a single-centre, open-label, non-randomised, dose-escalation phase 1 trial in China report that the vaccine was immunogenic, inducing humoral responses (peaking 28


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days after vaccination) and T-cell responses (peaking 14 days after vaccination) in most participants. Participants were healthy and had no underlying diseases. At least one adverse reaction was reported within the first 7 days after vaccination in 83% (low- and medium-dose groups) and 75% (high-dose group) of participants. The most common adverse reactions reported included injection-site reactions, fever, fatigue, headache, and muscle pain. No serious adverse events were noted within 28 days of vaccination.[334] A phase 2 randomised, double-blind, placebo-controlled trial in around 500 healthy adults (50% male, mean age 39 years) found that the vaccine induced a significant immune response in the majority of patients after a single dose of either the $1x10^{11}$ or the $5x10^{10}$ viral particle dose at day 28. Adverse reactions were significantly higher in the Ad5-nCoV group compared with placebo, and were reported in 72% of participants in the $1x10^{11}$ viral particle dose group and 74% of participants in the $5x10^{10}$ viral particle dose group.[335]

- ChAdOx1 nCoV-19: an adenovirus vector vaccine that carries the SARS-CoV-2 spike protein. Preliminary results (not peer reviewed) from animal studies found that a single dose induced a humoral and cellular response in mice and rhesus macaques. However, while viral loads in bronchoalveolar lavage fluid and lung tissues of vaccinated animals were significantly reduced compared with unvaccinated animals, reduction in viral shedding from the nose was not observed.[336] A phase 1/2, single-blind, randomised controlled trial in young healthy volunteers that used the meningococcal conjugate vaccine as a control found that ChAdOx1 nCoV-19 was immunogenic. Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group and no serious adverse events were reported in the 28 days following vaccination.[337]
- Inactivated SARS-CoV-2 virus (Sinovac®): contains a more traditional chemically inactivated version of the virus. The vaccine was found to induce immunity in mice, rats, and non-human primates. When challenged with the virus, monkeys who were vaccinated with the highest dose of the vaccine did not develop infection, and no virus was recovered from the throat, lung, or rectum.[338] In an interim analysis of two ongoing randomised controlled trials in healthy adults aged 18 to 59 years, a phase 1 trial of 96 participants and a phase 2 trial of 224 participants, the vaccine induced a neutralising antibody response by 14 days. The studies compared the vaccine with an alum adjuvant. The incidence of adverse effects across all participants within 7 days of injection was 15%, most commonly injection-site reactions and fever. Although the vaccine elicited an antibody response, it is unknown whether this could protect individuals against COVID-19.[339]
- mRNA-1273: a novel vaccine that uses mRNA technology not previously approved for use in humans. The mRNA encodes for a full-length prefusion stabilised spike protein of SARS-CoV-2 and is encapsulated in a lipid nanoparticle. Results from a phase 1 trial indicated that all 45 healthy adults (ages 18-55 years) who were given 2 injections (25, 100, or 250 micrograms) of the vaccine 28 days apart seroconverted by day 15 after the first dose. All dose groups had antibody levels in the top quartile for convalescent serum after the second vaccination. Systemic adverse events occurred more frequently after the second vaccination and occurred in 54% of participants in the 25-microgram group, and 100% of participants in the 100-microgram and 250-microgram groups. Of the cohort of 14 patients who received the highest dose (250 micrograms), 21% of participants experienced one or more severe adverse events following the second dose. One participant in the 25-microgram group was withdrawn due to transient urticaria related to the first vaccination. The study did not include people with underlying conditions.[340] mRNA-1273 has been granted fast-track designation by the US Food and Drug Administration (FDA), and phase 3 trials have started.
- BNT162b1: a lipid nanoparticle-formulated, nucleoside-modified, mRNA vaccine that encodes spike glycoprotein RBD. Preliminary (not peer reviewed) phase 1/2 study results in healthy adults aged 18 to 55 years have been published. RBD-binding immunoglobulin G antibodies and SARS-CoV-2 neutralising antibodies were detected in all subjects at 28 days after two doses. Adverse reactions were dose-dependent and reported in 50% of subjects who received the 10 microgram or 30 microgram dose, and by 58% of subjects who received the 100 microgram dose.[341] BNT162b1 and BNT162b2 (its related vaccine candidate) have been granted fast-track designation by the FDA. A global phase 2/3 trial of BNT162b2 has started.
- Results from other vaccine candidates are becoming available; however, a detailed discussion of all vaccine candidates is beyond the scope of this topic.
- The FDA has issued guidance to vaccine developers that in order for it to approve a vaccine candidate the primary efficacy end-point point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy end-point point estimate is >30%.[342]

Immunity passports

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- 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.[343] 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.[344]

Smoking cessation

- Past or current smokers have nearly double the risk for severe disease, and smoking cessation should be encouraged.[345] The WHO recommends that tobacco users stop using tobacco given the well-established harms associated with tobacco use and second-hand smoke exposure.[247] Public Health England also recommends stopping smoking. [Public Health England: COVID-19 – advice for smokers and vapers]



# Screening

## Management of contacts

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:[495]

- Face-to-face contact with a probable or confirmed case within 1 metre (3 feet) 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.

Contacts should remain in quarantine at home and monitor their health for 14 days from the last day of possible contact with the infected person. Local surveillance guidelines should be followed.

## Screening of travellers

Exit and entry screening may be recommended in countries where borders are still open, particularly when repatriating nationals from affected areas. Travellers returning from affected areas should self-monitor for symptoms for 14 days and follow local protocols of the receiving country. Some countries may require travellers to enter mandatory quarantine in a designated location (e.g., a hotel). Travellers who develop symptoms are advised to contact their local healthcare provider, preferably by phone.[496] 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.[497]

## Drive-through screening centres

Drive-through screening centres 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, examination, 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.[498]


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## 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.[499]



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# Case history

## Case history #1

A 61-year-old man presents to 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 examination, his pulse is 120 bpm, his temperature is 38.7°C (101.6°F), 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 empirical antibiotics. 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 develops respiratory distress 7 days after admission and is transferred to the intensive care unit and started on mechanical ventilation.

## Case history #2

A 26-year-old woman calls her doctor complaining of a sore throat and a persistent dry cough. She denies having a fever, and has not travelled in the last 14 days or knowingly been in contact with a confirmed case of COVID-19. She is advised to stay at home and self-isolate and to call her doctor if her symptoms get worse.

# Step-by-step diagnostic approach

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

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.[2] Immediately isolate all suspected and confirmed cases and implement local infection prevention and control procedures. Triage patients with a standardised triage tool and evaluate the patient to assess the severity of disease. COVID-19 is a notifiable disease. Suspected cases should remain in the pathway until proven negative.

Best Practice has published a separate topic on the management of co-existing conditions in the context of COVID-19. [BMJ Best Practice: Management of co-existing conditions in the context of COVID-19]

## 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.[2]
- 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




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or community transmission and contacts of probable and confirmed cases are at higher risk of infection.[166]

- Suspect the diagnosis in patients with a new continuous cough, fever, or altered sense of taste or smell.[346] Patients may also present with symptoms including dyspnoea, fatigue, myalgia/arthralgia, sore throat, headache, nasal congestion or rhinorrhoea, sputum production, chest tightness, or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).[347]
- Order real-time reverse transcription polymerase chain reaction (RT-PCR) to confirm the diagnosis. Take upper respiratory specimens in ambulatory patients, and/or lower respiratory specimens in patients with more severe disease.[348] Serological testing is not currently recommended outside of research settings.[349]
- 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.[350] 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.[351]
- Order the following laboratory investigations in hospitalised patients: full 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.
- Prioritise a chest x-ray in patients who are seriously ill with suspected pneumonia. Consider a computed tomography scan of the chest if chest x-ray is uncertain or normal.[352] Consult local guidelines.
- Report all suspected or confirmed cases to your local health authorities. COVID-19 is a notifiable disease.
- 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.

Diagnosis should be suspected in:[166]

- People residing or working in an area with a high risk of transmission (e.g., closed residential settings, humanitarian setting), people residing in or travelling 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 1 metre (3 feet) 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.



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## Clinical presentation in adults

Approximately 15% of patients present with the symptom triad of fever, cough, and dyspnoea, and 90% present with more than one symptom.[32] Some patients may be minimally symptomatic or asymptomatic, while others may present with severe pneumonia or complications such as acute respiratory syndrome, septic shock, acute myocardial infarction, venous thromboembolism, or multi-organ failure.

The most common symptoms are:

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

Less common symptoms include:

- Myalgia or arthralgia
- Fatigue
- Sputum production
- Chest tightness
- Gastrointestinal symptoms
- Sore throat
- Dizziness
- Headache
- Neurological symptoms
- Cutaneous symptoms
- Rhinorrhoea/nasal congestion
- Chest pain
- Ocular symptoms
- Haemoptysis.

Signs and symptoms of febrile respiratory illness may not possess the necessary sensitivity for early diagnostic suspicion.[353] A Cochrane review found that at least half of patients had a cough, sore throat, fever, myalgia/arthralgia, fatigue, or headache. 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.[347]

The clinical presentation has varied slightly across geographical 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.[354] Data from the first hospitalised patients in New York found that while the most common presenting symptoms were fever, cough, dyspnoea, and myalgia, gastrointestinal symptoms appeared to be more common than in China.[355]

In terms of severity:[4]




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- 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.

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, rhinorrhoea, 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.[356]

Pregnant women

- The clinical characteristics in pregnant women are similar to those reported for non-pregnant adults.[357] It is important to note that symptoms such as fever, dyspnoea, gastrointestinal symptoms, and fatigue may overlap with symptoms due to physiological adaptations of pregnancy or adverse pregnancy events.[2]

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.[2]
- 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as yet.[358] [359] [360] [361]

Co-infections

- Bacterial co-infections have been reported in 7% of hospitalised patients, and 14% of patients in intensive care units. The most common bacteria were *Mycoplasma pneumoniae* , *Pseudomonas aeruginosa* , *Haemophilus influenzae* , and *Klebsiella pneumoniae* . Co-infections with fungal pathogens and viruses (e.g., respiratory syncytial virus, influenza A) were less commonly reported.[362]
- Co-infections are more common in critically ill patients.[363]
- Co-infections may be associated with protracted respiratory symptoms, prolonged intensive care stay, morbidity, and mortality if not detected and treated early.[364]
- Patients with influenza co-infection showed similar clinical characteristics to patients with COVID-19 only.[365] [366]

## 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.

In terms of severity:[367]

- 33% of children present with mild illness
- 51% of children present with moderate illness



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- 7% of children present with severe illness
- 5% of children present with critical illness
- 20% of children present with asymptomatic illness.

Evidence so far suggests a milder, or asymptomatic, course of disease in about 95% of children, but with possible evidence of radiological lung changes in both categories. Symptoms commonly reported include fever, cough, sore throat, nasal congestion, and rhinorrhoea. Fever, cough, and dyspnoea are less common in children compared with adults. Children may present with gastrointestinal symptoms more commonly than adults, particularly newborns and infants, and they may be the only symptom.[350] Febrile seizures have been reported rarely.[9] The clinical manifestations in children under 5 years of age appear to be milder compared with those of influenza A infection.[368]

Severe disease has been reported rarely in children.[350] [369] In a cross-sectional study of 48 critically ill infants and children in the US, the clinical course and hospital outcomes were better compared with adults. Similar to adults, 80% of critically ill children had pre-existing comorbidities, most commonly immune suppression/cancer, obesity, and diabetes.[370] It is worth noting that critical disease has been reported more frequently in children under 1 year of age compared with children older than 1 year of age, and vomiting is more common in this age group.[367] There is increasing concern that a related inflammatory syndrome is emerging in children with severe disease. See the Complications section for more information.

Cases of COVID-19 have been reported in neonates. Dyspnoea is the most common sign in neonates. Although illness is usually mild, severe illness, including cases of late-onset neonatal sepsis and encephalitis, has been reported. Severe illness is slightly more common in neonates compared with older children. Infants may present with irritability, crying, feeding difficulties, silent hypoxia, and neurological symptoms.[350] [371] [372] [373]

Co-infections may be more common in children.[374] Co-infection 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* .[375] [9]



## Physical examination

Perform a physical examination. 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, tachypnoea, or cyanosis accompanying hypoxia. Bradycardia has been noted in a small cohort of patients with mild to moderate disease.[376]

## Pulse oximetry

Pulse oximetry may reveal low oxygen saturation ($SpO_2$ <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. Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognising further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[377]


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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.[378]

## Initial laboratory investigations

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

- ABG
- FBC
- 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.

The most common laboratory abnormalities are lymphopenia, leukocytosis, leukopenia, thrombocytopenia, decreased albumin, elevated cardiac biomarkers, elevated inflammatory markers, elevated D-dimer, and abnormal liver and renal function.[355] [379] [380] [381] Laboratory abnormalities – in particular, lymphopenia, leukocyte abnormalities, and other markers of systemic inflammation – are less common in children.[350] [382] [383] 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.[384]

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 epidemiological history. Specimens should be collected prior to starting empirical antimicrobials if possible.[2]

**[VIDEO: Radial artery puncture animated demonstration ]**

## Molecular testing

Molecular testing is required to confirm the diagnosis. Diagnostic tests should be performed according to guidance issued by local health authorities and should adhere to appropriate biosafety practices. If testing is not available nationally, specimens should be shipped to an appropriate reference laboratory. Specimens for testing should be collected under appropriate infection prevention and control procedures.

Decisions about who to test should be based on clinical and epidemiological factors. Consult local health authorities for guidance as testing priorities will depend on local guidelines and available resources. When resources are limited, certain groups of people may need to be prioritised for testing. In the UK, testing is recommended in all people with symptoms of new continuous cough, high temperature, or altered sense of smell/taste.[346] In the US, the Centers for Disease Control and Prevention has published detailed testing recommendations, including testing guidance for nursing homes and long-term care facilities, and essential workers who have been exposed.[385]

Perform a nucleic acid amplification test, such as real-time reverse-transcription polymerase chain reaction (RT-PCR), for SARS-CoV-2 in appropriate patients with suspected infection, with confirmation by nucleic acid sequencing when necessary.[348]



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- Collect upper respiratory specimens (nasopharyngeal and oropharyngeal swab or wash) in ambulatory patients and/or lower respiratory specimens (sputum and/or endotracheal aspirate or bronchoalveolar lavage) in patients with more severe respiratory disease. Consider the high risk of aerolisation when collecting lower respiratory specimens.
- Also consider collecting additional clinical specimens (e.g., blood, stool, urine).

Interpret results with caution. RT-PCR detects RNA but it is not fully understood how that represents infectious virus, which ultimately could lead to restrictions for people who do not present an infection risk. 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.[386] 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.[387]

Interpreting the test result depends on the accuracy of the test, and the pretest probability (or estimated risk of disease) before testing. A positive result holds more weight than a negative test due to the test's high specificity (around 95%) but moderate sensitivity (around 70%).[388]

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.[389]

There is a lack of data on the rate of false-positive tests. False-positive results are more likely when the prevalence of SARS-COV-2 is moderate to low.[390] False-positive results can be caused by cross-reaction with antibodies formed by current and past exposure to seasonal human coronavirus infections (e.g., common cold).[391]

False-negative rates of between 2% and 29% have been reported.[388] 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.[392]

One or more negative results do not rule out the possibility of infection. If a negative result is obtained from a patient with a high index of suspicion for COVID-19 (or a high pretest probability), additional specimens should be collected and tested, especially if only upper respiratory tract specimens were collected initially.[348] There is a case report of a patient who returned two consecutive negative results and didn't test positive until 11 days after symptom onset and confirmation of typical chest computed tomography (CT) findings.[393]

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 co-infections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19.[2] [394]




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## Serological testing

Serological testing is becoming increasingly available for use; however, while rapid antibody detection kits have been approved for the qualitative detection of SARS-CoV-2 immunoglobulin G (IgG)/IgM antibodies in serum, plasma, or whole blood, the World Health Organization (WHO) does not recommend the use of these tests outside of research settings as they have not been validated as yet.[349]

Evidence is particularly weak for point-of-care serological tests. A meta-analysis found that the overall sensitivity of chemiluminescent immunoassays (CLIAs) for IgG or IgM was approximately 98%, and the sensitivity of enzyme-linked immunosorbent assays (ELISAs) was 84%; however, lateral flow immunoassays (LFIAs), which have been developed as point-of-care tests, had the lowest sensitivity at 66%. Test sensitivity was highest 3 or more weeks after onset of symptoms. Available evidence does not support the use of existing point-of-care serological tests.[395]

The US Centers for Disease Control and Prevention recommends that serological assays that have received emergency-use authorisation from the Food and Drug Administration are preferred. There is no advantage of assays whether they test for IgG, IgM and IgG, or total antibody. The test's positive predictive value should be optimised 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). Testing can be used to aid the diagnosis of patients who present 9 to 14 days after symptom onset in addition to other viral detection methods, or as a method to help support a diagnosis in patients who present with late complications. Serological 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.[396]

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.[397] [398] 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).[399]

Serum samples can be stored to retrospectively define cases when validated serology tests become available.

## 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.[400]

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.[31] [32] [401] 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.[402]

Consider ordering a CT scan of the chest. CT imaging is the primary imaging modality in some countries, such as China. It may be helpful in making the diagnosis, guiding individual patient management



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decisions, aiding the diagnosis of complications, or giving clues to an alternative diagnosis. 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 non-specific 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.[352]

[BSTI: radiology decision tool for suspected COVID-19]

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.[403]

The American College of Radiology recommends reserving CT for hospitalised, symptomatic patients with specific clinical indications for CT, and emphasises 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.[404]

Abnormal chest CT findings have been reported in up to 97% of COVID-19 patients in one meta-analysis of 50,466 hospitalised patients.[405] Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[406] CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients.[92] [407] More than half of patients with asymptomatic disease present with CT abnormalities.[384] Some patients may present with a normal chest finding despite a positive RT-PCR.[408] 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.[409]

Typical features

- The most common findings are ground-glass opacity, either in isolation or co-existing 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.[410]
- 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.[410]
- 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.[411]
- Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity and, less frequently, non-specific 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.[412]

Atypical features




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- 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.[410]

The WHO recommends chest imaging in the following scenarios:[402]

- 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 hospitalised and have mild symptoms (to decide on hospital admission versus home discharge)
- Patients with suspected or confirmed COVID-19 who are not currently hospitalised 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 hospitalised 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.[413] [414] [415]

Antigen testing

- In the US, the Food and Drug Administration has issued an emergency-use authorisation for the first COVID-19 antigen test. These tests detect fragments of proteins found on or within the virus by testing samples collected from nasal cavity swabs. The test works faster than RT-PCR; however, while it is very specific for the virus, it is not as sensitive, so a negative result should be followed up with a RT-PCR test.[416]

Lung ultrasound

- Lung ultrasound is used as a diagnostic tool in some centres 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.[402] It has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, easier sterilisation process, absence of ionising 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.[417] May be used in pregnant women and children.[418] [419]
- [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas]



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# Risk factors

## Strong

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

- People residing or working in an area with a high risk of transmission (e.g., closed residential settings, humanitarian setting), people residing in or travelling 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.[166]

### contact with 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 1 metre (3 feet) 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.[166]

### older age

- Older age is a risk factor for infection.[167] Data from a cross-sectional study in the UK indicate 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.[168] The risk of severe illness in adults increases with age, with older people (aged 65 years and older) at highest risk.[169] [170] The highest mortality rate has been observed in patients 80 years and older.[171] In the US, patients ≥65 years accounted for 31% of all cases, 45% of hospitalisations, 53% of intensive care unit admissions, and 80% of deaths, with the highest incidence of severe outcomes in patients aged ≥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.

### residence in a long-term care facility

- Widespread transmission has been reported in long-term care facilities.[59] People who live in a nursing home or long-term care facility are at higher risk for severe illness.[170] Care home residents represent approximately one third of the total number of deaths in England and Wales; other countries have reported a similar experience. This is likely due to shortages in personal protective equipment, a vulnerable population, and a lack of testing.[172] More than one third of care homes in England have had cases.[173] A study across four nursing homes in the UK 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and of these, 43% were asymptomatic and 18% had atypical symptoms.[174]

### male sex

- Male sex is a risk factor for infection, more severe disease, worse prognosis, and mortality.[175] Data from a cross-sectional study in the UK found that the adjusted odds of a positive test were greater in males (18.4%) compared with females (13.3%).[168] It has been hypothesised that this may be due to the presence of androgens, or a lower level of SARS-CoV-2 antibodies compared with females; however, further research is required.[176] [177]





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### ethnicity

- People from Black, Asian, and minority ethnic (BAME) groups are at a higher risk of infection and worse outcomes, including an increased risk of mortality, compared with the general population. The reasons for this are unclear and require further research.[178] Data from a cross-sectional study in the UK found that the adjusted odds of a positive test were greater in Black people (62.1%) compared with White people (15.5%).[168] The average age of patients from ethnic minorities was significantly lower than that of White patients.[179] 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.[180] There is also evidence from the US that supports this. Age-adjusted data from the Centers for Disease Control and Prevention (as of 25 June) show that non-Hispanic American Indian, Alaska Native, and non-Hispanic Black people have approximately 5 times the rate of hospitalisations of non-Hispanic White people, and Hispanic or Latino people have approximately 4 times the rate of hospitalisations of non-Hispanic White people.[181] However, a cohort study of over 11,000 patients across 12 states in the US found there was no difference in all-cause, in-hospital mortality between Black and White patients after adjusting for sociodemographic factors and comorbidities (e.g., age, sex, insurance).[182] In a study of over 10,000 deceased patients in the US, 35% of Hispanic and 30% of non-White decedents were aged <65 years, compared with 13% of White, non-Hispanic decedents.[183]

### presence of comorbidities

- People with comorbidities are at higher risk for severe illness and mortality.[184] The more comorbidities a person has, the greater their risk for severe illness.[185] The most prevalent comorbidities in adults with COVID-19 are hypertension, diabetes, chronic respiratory disease, cardiovascular disease, and other chronic diseases such as cancer.[186] In a prospective observational cohort study of more than 20,000 hospitalised patients in the UK, the most common comorbidities were chronic cardiac disease (31%), uncomplicated diabetes (21%), non-asthmatic chronic pulmonary disease (18%), and chronic kidney disease (16%).[6] Similarly, in the US the most common comorbidities were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Hospitalisations were six times higher and deaths were 12 times higher in patients with comorbidities compared with those without.[187] It has been estimated that approximately 56% of adults in the US are at risk for requiring hospitalisation from COVID-19 because of the presence of at least one comorbidity. These underlying conditions are associated with modifiable risk factors, which, if improved through lifestyle changes, may improve a person's risk status.[188]
- Among 345 paediatric cases with information on underlying conditions, 23% had at least one underlying condition, most commonly chronic lung disease, cardiovascular disease, or immunosuppression.[189] Approximately 39% of hospitalised children had an underlying condition in another study. The most prevalent comorbidities were asthma, neurological disorders, diabetes, obesity, cardiovascular disease, and malignancy/haematological conditions.[190]
- Around 32% of young adults (aged 18-25 years) in the US had underlying conditions that put them at risk for severe disease including heart conditions, diabetes, asthma, immune conditions, liver conditions, and obesity. Smoking (including e-cigarette use) in the past 30 days also increased the risk. The rate of young adults at risk for severe disease decreased to 16% when considering non-smokers only.[191]



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### cardiovascular disease

- People with serious heart conditions (e.g., heart failure, coronary artery disease, cardiomyopathy, pulmonary hypertension) are at increased risk of severe illness.[185] Cardiovascular disease is associated with a 3-fold increased odds of severe infection, and an 11-fold increase in all-cause mortality.[192]

### hypertension

- People with hypertension may be at increased risk of severe illness.[185] 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.[193] Patients with hypertension have a 2.27-fold higher risk of severe disease, and a 3.48-fold higher risk of fatality compared with patients without hypertension.[194]

### diabetes

- People with type 2 diabetes are at increased risk of severe illness. People with type 1 diabetes or gestational diabetes may also be at increased risk of severe illness; however, evidence is limited for these patient groups.[185] The pooled prevalence of diabetes in COVID-19 patients is approximately 10%. Prevalence is significantly higher in older patients and patients with severe disease.[195] [196] [197] Diabetes is associated with increased risk of mortality, disease progression, and acute respiratory distress syndrome.[198] Patients with diabetes have a 2-fold higher risk of developing severe disease, and a 2-fold higher risk of mortality.[196] 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 haemoglobin (HbA1c) levels, higher body mass index, elevated C-reactive protein, and insulin use.[199] [200] However, HbA1c levels were not associated with mortality in a large US cohort of hospitalised patients with diabetes and COVID-19, while insulin treatment and obesity were strong and independent risk factors for in-hospital mortality.[201] Patients with poorly controlled hyperglycaemia have an increased risk of disease severity and mortality.[202] [203] Hyperglycaemia at admission is an independent risk factor for poor prognosis in hospitalised patients.[204] One third of all deaths in hospitalised patients in England occur in patients with diabetes. People with type 1 diabetes have 3.50 times the odds of dying in hospital with COVID-19, while people with type 2 diabetes have 2.03 times the odds.[205] Patients with newly diagnosed diabetes have a higher risk of all-cause mortality compared with patients with known diabetes, hyperglycaemia, or normal glucose.[206] The poor prognosis in these patients is likely due to the syndromic nature of diabetes, with factors such as hyperglycaemia, older age, and the presence of comorbidities (e.g., obesity, hypertension, cardiovascular disease) all contributing to the increased risk.[207]

### chronic respiratory disease

- There is no clear evidence that people with asthma or chronic obstructive pulmonary disease (COPD) are at higher risk of infection.[208] [209] People with COPD (including emphysema and chronic bronchitis) are at increased risk of severe illness.[185] COPD is associated with a 5-fold increased risk of severe infection.[210] It is unclear whether patients with asthma have a higher risk for severe disease; however, there is no statistically significant association between asthma and a higher risk of mortality in patients with COVID-19.[211] [212] [213] People with other chronic lung diseases (e.g., cystic fibrosis, idiopathic pulmonary fibrosis) may be at increased risk of severe illness; however, the evidence is limited.[185] There are no data on whether paediatric respiratory diseases (including childhood asthma) are risk factors for infection or severity.[214]




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### chronic kidney disease

- People with chronic kidney disease may be at higher risk of infection. Data from a cross-sectional study in the UK 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%).[168] People with chronic kidney disease are also at increased risk of severe illness.[185] The prevalence of pre-existing chronic kidney disease in COVID-19 patients was 5.2% (2.3% for end-stage kidney disease), and is an independent risk factor for developing acute kidney injury as a complication.[215]

### malignancy

- People with cancer are at a higher risk of infection, likely due to immunosuppressive treatments and/or recurrent hospital visits.[216] The overall pooled prevalence of cancer in COVID-19 patients is approximately 2.3%, and it is significantly associated with severe disease.[217] Patients with cancer are 76% more likely to get severe disease compared with those without cancer.[218] They also have an increased risk of worse clinical outcomes including intensive care unit admission and all-cause mortality (particularly those with metastatic disease, haematological cancer, or lung cancer), and appear to deteriorate more quickly compared with patients without cancer.[219] [220] Patients with haematological malignancies, in particular, have a higher risk of severe or critical disease and a high mortality rate.[221] The odds ratio of intensive care admission rates and mortality rates between cancer and non-cancer groups was 2.88 and 2.25, respectively.[222] Patients who underwent cancer surgery had higher mortality rates.[223] Factors associated with an increased mortality rate in adults include older age, male sex, smoking status, number of comorbidities, Eastern Cooperative Oncology Group performance status of 2 or more, receiving chemotherapy within 4 weeks before symptom onset, and active cancer.[224] [225] [226] However, a subgroup analysis of patients aged 65 years and older found that all-cause mortality was comparable to patients without cancer.[220] Children with cancer may be no more vulnerable to infection compared with children without cancer. Limited data show that the overall morbidity in paediatric patients with cancer is low, with only 5% requiring hospitalisation for symptoms.[227] Pooled case fatality rates of between 6.8% and 21% have been reported in adults with cancer, although these rates should be interpreted with caution.[228]

### obesity

- People with obesity (body mass index ≥30) are at higher risk of infection. Data from a cross-sectional study in the UK found that the adjusted odds of a positive test were greater in patients with obesity (20.9%) compared with those without (13.2%).[168] People with obesity are also at increased risk of severe illness.[185] [229] Data from France estimates that the prevalence of obesity is 1.35 times higher in patients with severe disease compared with the general population.[230] Obesity is a risk factor for intensive care admission, respiratory failure leading to invasive mechanical ventilation, and mortality.[231] [232] Obesity plays a significant role in the risk of death from COVID-19, particularly in males and younger people (<60 years of age).[233] Increased body mass index is a significant risk factor for severe disease in pregnant women.[234] Obesity was the most common comorbidity in children, and was significantly associated with mechanical ventilation in children 2 years and older in a single-centre retrospective study in New York.[235]

### sickle cell disease

- People with sickle cell disease are at increased risk of severe illness; people with other haemoglobin disorders (e.g., thalassaemia) may be at increased risk of severe illness.[185] Among 178 patients with sickle cell disease and COVID-19 in the US (mean patient age <40 years), 69% were



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hospitalised, 11% were admitted to intensive care, and 7% died.[236] Infection can cause acute chest syndrome in patients with sickle cell disease.[237] [238]

### solid organ transplant

- People with an immunocompromised state from solid organ transplant are at increased risk of severe illness.[185] Organ transplant recipients may be at higher risk of severe illness or complications, more rapid clinical progression, and a prolonged clinical course compared with the general population due to chronic immunosuppression and the presence of co-existing conditions.[239] [240] [241] [242] [243] [244]

### smoking

- Patients with any smoking history are at higher risk of severe disease and worse in-hospital outcomes. Current smokers have an increased risk of severe or critical disease. Patients with a smoking history have a significantly increased risk of severe or critical disease, in-hospital mortality, disease progression, and need for mechanical ventilation.[245] This may be due to increased airway expression of the angiotensin-converting enzyme-2 receptor in smokers.[246] The World Health Organization has reviewed the available evidence and concluded that smoking is associated with increased severity of disease and death in hospitalised patients.[247]

### cerebrovascular disease

- The pooled prevalence of pre-existing cerebrovascular disease in COVID-19 patients is 4.4%. Patients with pre-existing cerebrovascular disease have 2.67-fold higher odds of poor outcomes including intensive care admission, mechanical ventilation, and mortality.[248]

### chronic liver disease

- The prevalence of chronic liver disease in COVID-19 patients is approximately 3%. The presence of chronic liver disease is associated with more severe disease and overall mortality.[249] 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.[250]

### dyslipidaemia

- Dyslipidaemia appears to be associated with an increased risk of severe disease according to one meta-analysis.[251]

### metabolic dysfunction-associated fatty liver disease

- Patients with severe COVID-19 may be more likely to have metabolic dysfunction-associated fatty liver disease (MAFLD; also called non-alcoholic fatty liver disease) compared with patients who have non-severe COVID-19.[252] MAFLD is associated with a 4- to 6-fold increase in severity of COVID-19.[253] Severity of COVID-19 has been associated with younger age (<60 years) and intermediate or high fibrosis-4 (FIB-4) scores in patients with MAFLD.[254] [255]

### surgery

- Surgical mortality and complications are higher in patients with COVID-19 compared with patients without COVID-19.[256] 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.[257] Postoperative pulmonary complications occur in half of patients with perioperative SARS-




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CoV-2 infection, and are associated with higher mortality, particularly in men and those aged 70 years and over.[258]

### pregnancy

- Pregnant women may be at increased risk of severe illness and adverse pregnancy outcomes.[185] According to an analysis of 8200 infected pregnant women, pregnant women were more likely to be hospitalised, to be admitted to the intensive care unit, and to receive mechanical ventilation compared with non-pregnant women; however, mortality rates did not differ.[18]

### immunosuppression

- People who are immunocompromised (e.g., HIV, blood or bone marrow transplant, immune deficiencies, prolonged use of corticosteroids or other immunosuppressant medications) may be at increased risk of severe illness; however, evidence is limited.[185] Patients with inflammatory bowel disease who were on long-term biologicals or other immunomodulatory therapies did not have a higher risk of poor outcomes; however, recent corticosteroid use may be related to worse outcomes.[259] Glucocorticoid exposure of ≥10 mg/day (prednisolone) has been associated with a higher odds of hospitalisation in patients with rheumatological disease.[260] HIV co-infection does not significantly impact presentation, hospital course, or outcomes of patients when compared with non-matched non-HIV patients.[261] People living with HIV who have well-controlled disease are not at risk of poorer disease outcomes compared with the general population. It is unclear whether those with poorly controlled disease or AIDS have poorer outcomes.[262]

## Weak

### air pollution

- Evidence suggests that there may be an association between long-term exposure to ambient air pollution and COVID-19.[263] [264] [265] [266] The highest numbers of cases were recorded in the most polluted regions of Italy, with patients presenting with more severe disease requiring intensive care. The mortality was 2-fold higher in polluted regions compared with other regions.[267] One study found that of deaths from COVID-19 across 66 administrative regions in Italy, Spain, France, and Germany, 78% of deaths occurred in just five regions, and these regions were the most polluted in terms of nitrogen dioxide levels.[268] A preprint study from Harvard University found that people who live in US regions with high levels of air pollution were more likely to die from COVID-19 than those who live in less polluted areas. The researchers found that an increase of 1 microgram/$m^3$ in fine particulate matter is associated with an 8% increase in the COVID-19 death rate.[269]

### climate and latitude

- Distribution of community outbreaks along restricted latitude, temperature, and humidity measurements are consistent with the behaviour of a seasonal respiratory virus.[270] Evidence suggests that cold and dry conditions may increase transmission, and warm and humid conditions may reduce the rate of infections; however, evidence is not yet sufficient to prove causation.[271] However, there is other evidence that suggests ambient temperature has no significant impact on transmission, especially during the pandemic stage of an emerging pathogen.[272] [273] [274] Further research is required on how weather conditions influence transmission as colder temperatures have been associated with increased transmission of other coronaviruses. Higher latitude may also be associated with an increased risk of cases and deaths in some countries.[275] A positive correlation has been



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found between lower death rates and a country's proximity to the equator, suggesting a correlation between sunlight exposure (and vitamin D levels) and reduced mortality.[276]

### residence in urban or deprived areas

- Data from a cross-sectional study in the UK found 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%).[168]

### vitamin D deficiency

- A population-based study in Israel found that patients who tested positive for COVID-19 had significantly lower plasma vitamin D levels compared with those who tested negative. Univariate analysis demonstrated an association between low plasma vitamin D level and increased likelihood of hospitalisation. The study concluded that low plasma vitamin D level appears to be an independent risk factor for COVID-19 infection and for hospitalisation.[277] A small retrospective observational preprint study (not peer reviewed) suggests a link between vitamin D insufficiency and COVID-19 severity.[278] However, further research is needed.[279] [280] [281] [282]

### ACE inhibitor/angiotensin-II receptor antagonist use

- There was originally concern that people on these drugs may be at increased risk of infection or more severe disease due to upregulation of angiotensin-converting enzyme-2 (ACE2) receptor expression.[283] However, high-certainty evidence suggests that use of these drugs is not associated with severe disease, and moderate-certainty evidence suggests that there is no association between the use of these medications and a positive SARS-CoV-2 test result among symptomatic patients.[284] A prospective cohort study of over 19,000 patients in England found that these drugs were associated with a significantly reduced risk of COVID-19, and were not associated with an increased risk of intensive care. However, variations between ethnic groups raise the possibility of ethnic-specific effects.[285] The UK National Institute for Health and Care Excellence states that conclusion cannot be drawn on whether these drugs increase or decrease the risk of developing COVID-19 or severe disease based on the current available evidence.[286] Professional societies recommend that patients who are already on these drugs continue to take them.[287] [288] [289]

### statin use

- There is concern that people on these drugs may be at increased risk of infection or more severe disease as statins have been shown to increase the expression of ACE2 in laboratory animals, and may promote the activation of the inflammatory pathway in acute respiratory distress syndrome leading to more severe disease.[283] However, a retrospective study of nearly 14,000 patients found that statin use was associated with a lower risk of all-cause mortality in patients with COVID-19, possibly due to the immunomodulatory effects of statins. Further research into the potential therapeutic or detrimental effects of statins is required.[290]

### autoimmune disease

- Autoimmune disease, in general, does not appear to be associated with a higher risk of infection.[291] [292] Patients with autoimmune rheumatic disease may be more susceptible to infection compared with the general population, although data are scarce.[293] Autoimmune disease has been associated with a slightly increased risk of disease severity and mortality; however, this was not statistically significant.[294] Risk of mortality appears to be associated with older age and the presence of




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comorbidities even in patients with autoimmune disease, rather than the autoimmune disease itself or use of immunosuppressive medications.[295] In patients with multiple sclerosis, neurological disability, age, and obesity were risk factors for severe disease.[296] Weak evidence suggests that people with inflammatory bowel disease may be somewhat protected from infection, likely due to their ongoing treatment for the condition.[297] Further research is required as there is concern about the risk of infection in these patients.

### neurological conditions

- People with neurological conditions (e.g., dementia) may be at increased risk of severe illness; however, evidence is limited.[185]

### thalassaemia

- People with thalassaemia may be at increased risk of severe illness; however, evidence is limited.[185]

### children with certain underlying conditions

- Children may be at increased risk of severe illness if they have certain conditions (e.g., obesity, diabetes, asthma and chronic lung disease, immunosuppression); are medically complex; have serious genetic, neurological, or metabolic disorders; or have congenital heart disease. However, evidence is limited.[185]

### blood group A#

- People with blood group A appear to be at increased risk of infection, while people with blood group O have a decreased risk.[298] 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.[299]

### gut dysbiosis

- There is some emerging evidence that gut microbiota dysfunction may be implicated in the pathogenesis of COVID-19, although this is yet to be confirmed. Patients appear to have a depletion of beneficial commensals ( *Eubacterium ventriosum* , *Faecalibacterium prausnitzii* , *Roseburia* and Lachnospiraceae taxa) and an overgrowth of opportunistic pathogens ( *Clostridium hathewayi* , *Actinomyces viscosus* , *Bacteroides nordii* ) during hospitalisation. Gut microbiome configuration has been associated with disease severity.[300] [301] [302]

# History & examination factors

## Key diagnostic factors

### fever (common)

- Reported in approximately 78% of patients.[420] Prevalence has been higher in some case series. In one case series, only 44% of patients had a fever on presentation, but it developed in 89% of patients after hospitalisation.[421] 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.[422]

### cough (common)



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- Reported in approximately 57% of patients.[420] Prevalence has been higher in some case series. The cough is usually dry; however, a productive cough has been reported in some patients.

### dyspnoea (common)

- Reported in approximately 23% of patients.[420] Prevalence has been higher in some case series. The World Health Organization estimates the range to be 31% to 40%.[2] Median time from onset of symptoms to development of dyspnoea is 5 to 8 days.[31] [32] [423] It is less common in children, but the most common sign in neonates.[350] May last weeks after initial onset of symptoms. Wheeze has been reported in 17% of patients.[420]

### altered sense of smell/taste (common)

- The pooled prevalence of olfactory dysfunction (anosmia/hyposmia) is 41%, with a pooled prevalence of 38% for gustatory dysfunction (ageusia/dysgeusia). Prevalence appears to be higher in European studies.[424] May be an early symptom before the onset of other symptoms, or may be the only symptom in patients with mild to moderate illness.[425] Complete resolution or improvement in symptoms was reported in 89% of patients 4 weeks after onset.[426]

## Other diagnostic factors

### fatigue (common)

- Reported in approximately 31% of patients.[420] Prevalence has been higher in some case series. 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.[420] Prevalence has been higher in some case series.

### sputum production/expectoration (common)

- Reported in approximately 23.7% of patients.[380] Prevalence has been higher in some case series.

### chest tightness (common)

- Reported in approximately 22.9% of patients.[380] Prevalence has been higher in some case series.

### sore throat (common)

- Reported in approximately 12% of patients.[420] Usually presents early in the clinical course.

### gastrointestinal symptoms (uncommon)

- Reported in 20% of patients. The weighted pooled prevalence of specific symptoms is as follows: loss of appetite 22.3%; diarrhoea 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.[427] Gastrointestinal symptoms are not associated with an increased likelihood for testing positive for COVID-19; however, anorexia and diarrhoea, when combined with loss of smell/taste and fever, were 99% specific for COVID-19 infection in one prospective case-control study.[428] Haematochezia has been reported.[429]

### dizziness (uncommon)




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- Reported in approximately 11% of patients.[420]

### headache (uncommon)

- Reported in approximately 13% of patients.[420]

### neurological symptoms (uncommon)

- Confusion has been reported in approximately 11% of patients.[420] Prevalence of confusion/delirium and agitation is high (65% and 69%, respectively) in patients in the intensive care unit.[430] Delirium is associated with an increased risk of mortality, and rapid onset may indicate clinical deterioration.[431] Anxiety, depression, and sleep problems have also been reported.[32]

### cutaneous symptoms (uncommon)

- Reported in 8.8% of patients with a positive test according to the UK COVID Symptom Study, with 17% of respondents reporting rash as the first symptom of disease, and 21% of respondents reporting rash as the only clinical sign.[432] Reported in 7.8% of hospitalised adults in one observational cross-sectional study in Italy.[433]
- Various manifestations have been reported in adults and children including a erythematous or maculopapular or morbilliform rash, a varicella-like papulovesicular exanthem on the trunk, petechiae, urticaria, vesicles, ischaemic and ecchymotic acral lesions as a manifestation of clotting disorders, pityriasis rosea, digitate papulosquamous eruption, and erythema multiforme-like lesions.[434] [435] [436] [437] [438] [439] [440] [441] [442]
- A case collection survey of images and clinical data classified lesions as: maculopapular eruptions (47%); acral areas of erythema with vesicles or pustules, or pseudo-chilblain (19%); urticarial lesions (19%); other vesicular eruptions (9%); and livedo or necrosis (6%). Vesicular lesions often appear early in the course of disease before other symptoms, and the pseudo-chilblain pattern frequently appears later in the course after the appearance of other symptoms.[443]
- Chilblains, particularly on the toes or foot, have been reported especially in younger patients who lack a history of chilblains, Raynaud's phenomenon, or collagen vascular diseases (e.g., systemic lupus erythematosus).[444] [445] [446] However, based on data from small case series, chilblains do not appear to be directly associated with COVID-19.[447] [448]
- 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 skin involvement.

### rhinorrhoea/nasal congestion (uncommon)

- Rhinorrhoea has been reported in approximately 8% of patients, and nasal congestion has been reported in approximately 5% of patients.[420]

### chest pain (uncommon)

- Reported in approximately 7% of patients.[420] May indicate pneumonia.

### ocular symptoms (uncommon)

- Reported in 11.2% of patients. The most common ocular symptom is unilateral or bilateral conjunctivitis. Other reported symptoms include ocular pain, dry eye, and floaters. Most symptoms are mild and last for 4 to 14 days with no complications. Prodromal symptoms occur in 12.5% of patients.[449]

### haemoptysis (uncommon)

- Reported in approximately 2% of patients.[420] May be a symptom of pulmonary embolism.[450]



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### bronchial breath sounds (uncommon)

- May indicate pneumonia.

### tachypnoea (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.





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# Diagnostic tests

## 1st test to order

| Test | Result |
|---|---|
| **real-time reverse transcription polymerase chain reaction (RT-PCR)**<br>• Molecular testing (with or without nucleic acid sequencing) is required to confirm the diagnosis.[348] Priorities for testing depend on local guidelines and available resources. Many different tests are available depending on geographical location. Home testing kits may be available in some locations.<br>• Collect upper respiratory specimens (nasopharyngeal and oropharyngeal swab or wash) in ambulatory patients and/or lower respiratory specimens (sputum and/or endotracheal aspirate or bronchoalveolar lavage) in patients with more severe respiratory disease. Also consider collecting additional clinical specimens (e.g., blood, stool, urine). Specimens should be collected under appropriate infection prevention and control procedures. Consider the high risk of aerolisation when collecting lower respiratory specimens.[348]<br>• The positive predictive value ranged from 47.3% to 96.4%, and the negative predictive value ranged from 96.8% to 99.9% in one meta-analysis. Pooled sensitivity was 89%.[451]<br>• Interpret results with caution. RT-PCR detects RNA but it is not fully understood how that represents infectious virus, which ultimately could lead to restrictions for people who do not present an infection risk.[386] Also, interpreting the test result depends on the accuracy of the test, and the pretest probability (or estimated risk of disease) before testing.[388] False-positive results are more likely when the prevalence of SARS-COV-2 is moderate to low, and can be caused by cross-reaction with antibodies formed by current and past exposure to seasonal human coronavirus infections (e.g., common cold).[390] [391]<br>• If a negative result is obtained from a patient with a high index of suspicion for COVID-19, additional specimens should be collected and tested, especially if only upper respiratory tract specimens were collected initially.[348]<br>• A point-of-care test that provides results within hours is available in some countries.[452] While rapid point-of-care tests are available, the World Health Organization does not recommend the use of these tests outside of research settings as they have not been validated as yet.[349] A pooled sensitivity of 64.8% and specificity of 98% has been reported with point-of-care tests.[453]<br>• Tests are available in many laboratories worldwide and testing should be done according to instructions from local health authorities and adhere to appropriate biosafety practices. If testing is not available nationally, specimens should be shipped to an appropriate reference laboratory.<br>• Collect nasopharyngeal swabs to rule out influenza and other respiratory infections according to local guidance. It is important to note that co-infections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19.[2] [394] A single-test multiplex assay to diagnose infection caused by influenza A, influenza B, and SARS-CoV-2 is available in the US.[454] | **positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA; may be positive for influenza A and B viruses and other respiratory pathogens** |



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| Test | Result |
|---|---|
| • There is emerging evidence that saliva may be a reliable specimen for detecting SARS-CoV-2 by RT-PCR.[455] [456] A test that uses saliva has been approved.[457] | |
| **pulse oximetry**<br>• Order in patients with severe illness.<br>• Recommended in patients with respiratory distress and cyanosis.<br>• 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. Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognising further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[377] | **may show low oxygen saturation ($SpO_2$ <90%)** |
| **ABG**<br>• Order in patients with severe illness as indicated to detect hypercarbia or acidosis.<br>• Recommended in patients with respiratory distress and cyanosis who have low oxygen saturation ($SpO_2$ <90%). | **may show low partial oxygen pressure** |
| **FBC**<br>• Order in patients with severe illness.<br>• Lymphopenia, leukocytosis, and thrombocytopenia are associated with severe disease; therefore, they may be useful as biomarkers for predicting disease progression.[458]<br>• High neutrophil-to-lymphocyte ratio is a useful marker for indicating risk for severe illness and poor prognosis.[459] [460]<br>• Absolute counts of major lymphocyte subsets, particularly CD4+ and CD8+ T-cell counts, are significantly decreased in patients with severe disease.[461]<br>• Late-phase thrombocytopenia (i.e., occurring 3 weeks or more after symptom onset) has been reported but is uncommon.[462] | **lymphopenia; leukocytosis; leukopenia; thrombocytopenia; decreased haemoglobin; decreased eosinophils#** |
| **comprehensive metabolic panel**<br>• Order in patients with severe illness.<br>• The most common laboratory abnormalities in patients hospitalised with pneumonia include elevated liver transaminases. Other abnormalities include decreased albumin and renal impairment.[31] [32]<br>• Elevated liver transaminases increase in severe disease; therefore, they may be useful as biomarkers for predicting disease progression.[463]<br>• Serum urea and creatinine levels increase in severe disease; therefore, they may be useful as biomarkers for predicting disease progression.[458]<br>• Hypoalbuminaemia is associated with severe disease and may be useful as a biomarker for predicting disease progression.[464]<br>• Hypokalaemia has been reported in 54% of patients.[465] Hypocalcaemia has been reported in 63% of patients.[466] Other electrolyte derangements may be present. | **elevated liver transaminases; decreased albumin; renal impairment; electrolyte derangements** |
| **blood glucose level**<br>• Order in patients with severe illness. | **variable** |




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| Test | Result |
|---|---|
| • Uncontrolled hyperglycaemia has been shown to worsen prognosis in all patients, not only patients with diabetes.[467] [468] [469] | |
| **coagulation screen**<br>• Order in patients with severe illness.<br>• The most common abnormalities are elevated D-dimer and fibrinogen, and prolonged prothrombin time.[31] [32] [423] [470]<br>• D-dimer levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[458] The risk of severe disease and mortality is 2-fold and 4-fold higher, respectively, in patients with elevated D-dimer levels.[471]<br>• Patients with very high D-dimer levels have an increased risk of thrombosis.[472] [473] | **elevated D-dimer; prolonged prothrombin time; elevated fibrinogen** |
| **serum C-reactive protein**<br>• Order in patients with severe illness.<br>• Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[458] [474] | **may be elevated** |
| **serum erythrocyte sedimentation rate**<br>• Order in patients with severe illness.<br>• Commonly elevated in patients with COVID-19.[381] | **may be elevated** |
| **serum lactate dehydrogenase**<br>• Order in patients with severe illness.<br>• Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[458]<br>• May be more common in patients with COVID-19 compared with other types of pneumonia.[411] | **may be elevated** |
| **serum interleukin-6 level**<br>• Order in patients with severe illness.<br>• Interleukin-6 is the most common cytokine released by activated macrophages. Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[458] [475] It is less likely to be elevated in children.[476] | **may be elevated** |
| **cardiac biomarkers**<br>• Order in patients with severe illness.<br>• Serum troponin I level may be elevated in patients with cardiac injury. Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[458]<br>• Other cardiac biomarkers (e.g., creatine kinase-myocardial band, brain natriuretic peptide, cardiac troponin T) may also be elevated and are associated with severe disease and worse outcomes.[477] [478]<br>• Creatine kinase-myocardial band has been found to be elevated in mild disease in children.[383] | **may be elevated** |
| **serum procalcitonin**<br>• Order in patients with severe illness.<br>• Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[479]<br>• May be elevated in patients with secondary bacterial infection.[31] [32] May be more common in children.[374]<br>• There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about the use of antibiotics.[480] | **may be elevated** |



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| Test | Result |
|---|---|
| • However, it may be helpful in limiting overuse of antibiotics in patients with COVID-19-related pneumonia.[481] | |
| **serum ferritin level**<br>• Order in patients with severe illness.<br>• May indicate development of cytokine release syndrome.[482] | **may be elevated** |
| **serum amyloid A level**<br>• Order in patients with severe illness.<br>• Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[458] | **may be elevated** |
| **serum creatine kinase**<br>• Order in patients with severe illness.<br>• Elevated creatine kinase has been reported in 13% to 33% of patients.[31] [32]<br>• Indicates muscle or myocardium injury. | **may be elevated** |
| **blood and sputum cultures**<br>• 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 epidemiological history.[2]<br>• Testing is most useful when there is concern for multidrug-resistant pathogens.[481]<br>• Specimens should be collected prior to starting empirical antimicrobials if possible. | **negative for bacterial infection** |
| **chest x-ray**<br>• Order in all patients with suspected pneumonia.<br>• Unilateral lung infiltrates are found in 25% of patients, and bilateral lung infiltrates are found in 75% of patients.[31] [32] [401]<br>• 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.[402] | **unilateral or bilateral lung infiltrates** |




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## Other tests to consider

| Test | Result |
|---|---|
| **computed tomography (CT) chest**<br>• Consider a CT scan of the chest. Consult local guidance on whether to perform a CT scan. The British Society of Thoracic Imaging (BSTI) recommends CT imaging in patients with clinically suspected COVID-19 who are seriously ill if chest x-ray is uncertain or normal. [BSTI: radiology decision tool for suspected COVID-19] 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.[403] The American College of Radiology recommends reserving CT for hospitalised, symptomatic patients with specific clinical indications for CT, and emphasises 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.[404]<br>• Abnormal chest CT findings have been reported in up to 97% of hospitalised patients.[405] Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[406] CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients.[92] [407] Some patients may present with a normal chest finding despite a positive RT-PCR.[408] 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.[409]<br>• The most common findings are ground-glass opacity, either in isolation or co-existing 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, vacuolar retraction sign, and halo sign are atypical features. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have also been reported rarely.[410]<br>• Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity and, less frequently, non-specific 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.[412]<br>• 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.[410]<br>• 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% and 37%, respectively.[451] A sensitivity of 96% has been reported in another meta-analysis.[483]<br>• In a cohort of over 1000 patients in a hyperendemic area in China, chest CT had a higher sensitivity for diagnosis of COVID-19 | **ground-glass opacity in isolation or co-existing with other findings (e.g., consolidation, interlobular septal thickening, crazy-paving pattern); bilateral, peripheral/subpleural, posterior distribution with a lower lobe predominance** |



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| Test | Result |
| --- | --- |
| 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.[484] [Fig-2] | |
| **serology**<br>• Serological testing is becoming increasingly available for use; however, 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 World Health Organization does not recommend the use of these tests outside of research settings as they have not been validated as yet.[349]<br>• Evidence is particularly weak for point-of-care serological tests. A meta-analysis found that the overall sensitivity of chemiluminescent immunoassays (CLIAs) for IgG or IgM was approximately 98%, and the sensitivity of enzyme-linked immunosorbent assays (ELISAs) was 84%; however, lateral flow immunoassays (LFIAs), which have been developed as point-of-care tests, had the lowest sensitivity at 66%. Test sensitivity was highest 3 or more weeks after onset of symptoms. Available evidence does not support the use of existing point-of-care serological tests.[395]<br>• The US Centers for Disease Control and Prevention recommends that serological assays that have received emergency-use authorisation from the Food and Drug Administration are preferred. There is no advantage of assays whether they test for IgG, IgM and IgG, or total antibody. The test's positive predictive value should be optimised 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). Testing can be used to aid the diagnosis of patients who present 9 to 14 days after symptom onset in addition to other viral detection methods, or as a method to help support a diagnosis in patients who present with late complications. Serological 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.[396]<br>• 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.[397] [398]<br>• 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).[399] | **positive for SARS-CoV-2 virus antibodies** |




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| Test | Result |
|---|---|
| • Serum samples can be stored to retrospectively define cases when validated serology tests become available. | |

## Emerging tests

| Test | Result |
|---|---|
| **antigen test**<br>• In the US, the Food and Drug Administration has issued an emergency-use authorisation for the first COVID-19 antigen test. These tests detect fragments of proteins found on or within the virus by testing samples collected from nasal cavity swabs. The test works faster than RT-PCR; however, while it is very specific for the virus, it is not as sensitive, so a negative result should be followed up with a RT-PCR test.[416] | **positive for SARS-CoV-2 virus antigen** |
| **reverse transcription loop-mediated isothermal amplification (RT-LAMP)**<br>• A similar process to RT-PCR, but uses constant temperatures and produces more viral DNA compared with RT-PCR. While simple and quick, it is a newer technology and there is less evidence for its use. Assays for SARS-CoV-2 have been developed and are being evaluated.[413] [414] [415] | **positive for SARS-CoV-2 viral RNA** |
| **lung ultrasound**<br>• Lung ultrasound is used as a diagnostic tool in some centres 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.[402]<br>• Has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, easier sterilisation process, absence of ionising 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.<br>• 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.[417]<br>• May be used in pregnant women and children.[418] [419]<br>• [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas] | **B-lines; pleural line abnormalities** |



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# Differential diagnosis

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| **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.<br>• 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.[485] [486] | • Blood or sputum culture or molecular testing: positive for causative organism.<br>• RT-PCR: negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA (co-infections are possible).<br>• CT chest: centrilobular nodules, mucoid impactions.[487] |
| **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.<br>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.<br>• 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.[488]<br>• Children more commonly affected.[488]<br>• A small case-control study found that new-onset smell and/or taste disorders were more common among patients with COVID-19 compared with patients with influenza.[489] | • RT-PCR: positive for influenza A or B viral RNA; negative for SARS-CoV-2 viral RNA (co-infections are possible).<br>• CT chest: there is emerging evidence that CT can be used for differentiating between influenza and COVID-19. COVID-19 patients are more likely to have rounded or linear opacities, crazy-paving sign, vascular enlargement, and interlobular septal thickening, but less likely to have nodules, tree-in-bud sign, bronchiectasis, and pleural effusion.[490] [491]<br>• 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.[492] |





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| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| **Common cold** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.<br>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. | • RT-PCR: positive for causative organism; negative for SARS-CoV-2 viral RNA (co-infections are possible). |
| **Other viral or bacterial respiratory infections** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.<br>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.<br>• Adenovirus and *Mycoplasma* should be considered in clusters of pneumonia patients, especially in closed settings such as military camps and schools. | • Blood or sputum culture of molecular testing: positive for causative organism.<br>• RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible). |
| **Aspiration pneumonia** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.<br>• Differentiating COVID-19 from aspiration pneumonia is not usually possible from signs and symptoms. | • RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).<br>• CT chest: difficult to distinguish on CT; however, anterior lung involvement may be more suggestive of COVID-19 pneumonia.[493] |
| **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.<br>• Differentiating COVID-19 from pneumocystis jirovecii pneumonia is not usually | • Sputum culture: positive for *Pneumocystis* .<br>• RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).<br>• CT chest: ground-glass opacity is usually more diffusely distributed with a tendency to spare the subpleural regions.[487] |



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| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| | possible from signs and symptoms.<br>• Patients are usually immunocompromised (e.g., HIV positive) and duration of symptoms may be longer. | |
| **Middle East respiratory syndrome (MERS)** | • Travel history to the Middle East or contact with a confirmed case of MERS.<br>• Differentiating COVID-19 from MERS is not possible from signs and symptoms.<br>• 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 epidemiological history as avian influenza H7N9 is endemic in China.<br>• Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area when avian influenza is endemic. | • RT-PCR: positive for H7-specific viral RNA. |
| **Avian influenza A (H5N1) virus infection** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.<br>• 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.<br>• History of symptoms is usually longer. | • 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 |




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| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| | • Presence of night sweats and weight loss may help to differentiate. | lymphadenopathy, and/or pleural effusion.<br>• Sputum acid-fast bacilli smear and sputum culture: positive.<br>• 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.[494]<br>• Symptoms of COVID-19 and neutropenic sepsis may be difficult to differentiate at initial presentation. | • CBC: neutropenia.<br>• RT-PCR: negative for SARS-CoV-2 viral RNA. |

# Diagnostic criteria

## Case definitions

Various case definitions are available:

- [WHO: public health surveillance for COVID-19 – interim guidance]
- [CDC: coronavirus disease 2019 (COVID-19) 2020 interim case definition]
- [PHE: COVID-19 – investigation and initial clinical management of possible cases]
- [ECDC: case definition for coronavirus disease 2019 (COVID-19)]



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# Step-by-step treatment 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; optimised supportive care; and organ support in severe or critical illness.

Best Practice has published a separate topic on the management of co-existing conditions in the context of COVID-19. [BMJ Best Practice: Management of co-existing conditions in the context of COVID-19]

## Key recommendations

- Consider whether the patient can be managed at home. Generally, patients with asymptomatic or mild disease can be managed at home or in a community facility.[2]
- 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.[2] [500]
- Provide symptom relief as necessary. This may include medications for fever, cough, breathlessness, anxiety, delirium, or agitation.[2] [501]
- Start supportive care according to the clinical presentation. This might include oxygen therapy, intravenous fluids, venous thromboembolism prophylaxis, high-flow nasal oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. Sepsis and septic shock should be managed according to local protocols.[2]
- Consider empirical antibiotics if there is clinical suspicion of 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.[2] [480]
- Consider low-dose dexamethasone in hospitalised patients who require oxygen or ventilation. Guidelines recommend this treatment based on results from the RECOVERY trial.[3] [502]
- Consider experimental therapies. Treatments such as remdesivir, hydroxychloroquine, lopinavir/ritonavir, and convalescent plasma therapy may be started according to local protocols.[2]
- 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.[2]
- 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.[2]

- 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.





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- 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.

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 aged 75 years and over), heart failure, male sex, chronic kidney disease, and increased body mass index (BMI).[503] The median time from onset of symptoms to hospital admission is around 7 days.[31] [423]

Children are less likely to require hospitalisation, but if admitted, generally only require supportive care.[189] [16] Risk factors for intensive care admission in children include age <1 month, male sex, pre-existing medical conditions, and presence of lower respiratory tract infection signs or symptoms at presentation.[504]

Overall, 19% of hospitalised patients require non-invasive ventilation, 17% require intensive care, 9% require invasive ventilation, and 2% require extracorporeal membrane oxygenation.[420] 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%.[505] The most common reasons for intensive care unit admission are hypoxaemic respiratory failure leading to mechanical ventilation and hypotension.[506] 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).[507] 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.[503]

## 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.[2]

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.[2] [3] This decision requires careful clinical judgement 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 carer is able to provide care and recognise when the patient may be deteriorating; the carer has adequate support (e.g., food, supplies, psychological support); the support of a trained health worker is available in the community.[495]

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).[2]



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- The US Centers for Disease Control and Prevention (CDC) recommends discontinuing home isolation once at least 10 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. In asymptomatic people, the CDC recommends discontinuing home isolation once at least 10 days have passed since the date of a positive test. Alternatively, it 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.[508] If the patient is hospitalised, 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.[509]

Infection prevention and control

- For patients in home isolation, advise patients and household members to follow appropriate infection prevention and control measures:
  - [WHO: home care for patients with suspected or confirmed COVID-19 and management of their contacts]
  - [CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19)]

Symptom management

- Fever and pain: paracetamol or ibuprofen are recommended.[2] [510] There is no evidence at present of severe adverse events in COVID-19 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[2] [501] [511] [512] [513] [514] [515] [516] 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 (e.g., a teaspoon of honey in patients aged 1 year and older) to help cough.[501] 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.[517]
- 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.[518]

Supportive care

- Advise patients about adequate nutrition and appropriate rehydration. Too much fluid can worsen oxygenation.[2]
- Advise patients to improve air circulation by opening a window or door (fans can spread infection and should not be used).[2] [501]
- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[2]

Monitor




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- 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).[2] [3]

## 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.[2]

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.[2] [3]

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.[2]
- The CDC recommends discontinuing isolation once at least 10 days (not severely immunocompromised) or 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 home isolation once at least 10 days (not severely immunocompromised) or 20 days (severely immunocompromised) have passed since the date of a positive test. Alternatively, it 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 in these patients.[519] 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 hospitalised patients, and 10 days in patients with milder disease who are managed in the community.[509]

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

- Consider empirical antibiotics if there is clinical suspicion of bacterial infection.[2] [3] Antibiotics may also be considered in older people (particularly those in long-term care facilities) and children <5 years of age to provide empirical antibiotic treatment for possible pneumonia.[2]

Monitor



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- 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). There is no evidence to support the use of pulse oximeters in the home setting.[2]
- 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.[2]

## Management of severe COVID-19#

Patients with suspected or confirmed severe disease are at risk of rapid clinical deterioration.[2]

- 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
    - $SpO_2$ <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 $SpO_2$ <90%
    - Severe respiratory distress
    - General danger sign
    - Inability to breastfeed or drink, lethargy or unconsciousness, or convulsions.

Location of care

- Manage patients in an appropriate healthcare facility under the guidance of a specialist team.[2]
- Assess all adults for frailty on admission to hospital, irrespective of age and COVID-19 status, using the Clinical Frailty Scale (CFS). [Clinical frailty scale] A large observational study found that disease outcomes were better predicted by frailty than either age or comorbidity; frailty (CFS score 5-8) was associated with earlier death and longer duration of hospital stay, and these outcomes worsened with increasing frailty after adjustment for age and comorbidity.[520]
- Involve critical care teams in discussions about admission to critical care for patients where:
    - The CFS score suggests the person is less frail (e.g., CFS <5), they are likely to benefit from critical care organ support, and the patient wants critical care treatment; or
    - The CFS score suggests the person is more frail (e.g., CFS ≥5), there is uncertainty regarding the benefit of critical care organ support, and critical care advice is needed to help the decision about treatment.
- Take into account the impact of underlying pathologies, comorbidities, and severity of acute illness.[500]

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.[2]
- The CDC recommends discontinuing isolation once at least 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. In asymptomatic people, the CDC recommends discontinuing isolation once at least 20 days have passed since the date of a positive test. Alternatively, it 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 in these patients.[519]
- 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 hospitalised patients.[509]

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 $SpO_2$ <90%.[2] [3] There is no evidence of benefit for oxygen therapy in patients with COVID-19 in the absence of hypoxaemia.[521]
- Target $SpO_2$ to ≥94% during resuscitation in adults and children with emergency signs who require emergency airway management and oxygen therapy. Once the patient is stable, a target $SpO_2$ >90% in children and non-pregnant adults, and ≥92% to 95% in pregnant women, is recommended. Nasal prongs or a nasal cannula are preferred in young children.[2] Some guidelines recommend that $SpO_2$ should be maintained no higher than 96%.[510]
- Some centres may recommend different $SpO_2$ targets in order to support prioritisation of oxygen flow for the most severely ill patients in hospital. NHS England recommends a target of 92% to 95% (or 90% to 94% if clinically appropriate), for example.[522]
- Consider positioning techniques (e.g., high supported sitting, prone position) and airway clearance management to assist with secretion clearance in adults.[2] Oxygen delivery can be increased by using a non-rebreathing mask and prone positioning.[523] Consider a trial of awake prone positioning to improve oxygenation in patients with persistent hypoxaemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated.[3] Early self-proning of awake, non-intubated patients has been shown to improve oxygen saturation and may delay or reduce the need for intensive care.[524] [525] [526] [527] [528]
- Monitor patients closely for signs of progressive acute hypoxaemic respiratory failure. Patients who continue to deteriorate despite standard oxygen therapy require advanced oxygen/ventilatory support.[2] [3]

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



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oxygenation.[2] Correct any electrolyte or metabolic abnormalities, such as hyperglycaemia or metabolic acidosis, according to local protocols.[529]

- Fever and pain: paracetamol or ibuprofen are recommended.[2] [510] There is no evidence at present of severe adverse events in COVID-19 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[2] [501] [511] [512] [513] [514] [515] [516] 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 (e.g., a teaspoon of honey in patients aged 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.[501] 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.[517]
- 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 oedema). Consider a trial of oxygen, if available. Consider an opioid and benzodiazepine combination in patients with moderate to severe breathlessness or patients who are distressed.[501]
- Anxiety, delirium, and agitation: identify and treat any underlying or reversible causes (e.g., offer reassurance, treat hypoxia, correct metabolic or endocrine abnormalities, address co-infections, minimise use of drugs that may cause or worsen delirium, treat substance withdrawal, maintain normal sleep cycles, treat pain or breathlessness).[2] [501] Consider a benzodiazepine for the management of anxiety or agitation that does not respond to other measures. Consider haloperidol or a phenothiazine for the management of delirium.[501] Low doses of haloperidol (or another suitable antipsychotic) can also be considered for agitation.[2] Non-pharmacological interventions are the mainstay for the management of delirium when possible, and prevention is key.[530]
- Mouth care: an important part of overall patient care in hospitalised patients who are ventilated or non-ventilated and those undergoing step-down or end-of-life care.[531]
- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[2]

Venous thromboembolism prophylaxis

- Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalised adults and adolescents with COVID-19 as per the standard of care for other hospitalised patients without COVID-19, provided there are no contraindications. A COVID-19 diagnosis should not influence a paediatrician's recommendations about VTE prophylaxis in hospitalised children. Pregnant women should be managed by a specialist.[2] [3] [532] [533]
- Low molecular weight heparin or fondaparinux are preferred over unfractionated heparin in order to reduce patient contact. Unfractionated heparin is contraindicated in patients with severe thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia. Direct oral anticoagulants are not recommended. Mechanical thromboprophylaxis (e.g., intermittent pneumatic compression devices) is recommended if anticoagulation is contraindicated or not available.[2] [533] [534]
- The optimal dose is unknown. Standard prophylaxis doses are recommended over intermediate- or full treatment-dose regimens.[533] Some clinicians are using intermediate- or full treatment-dose regimens rather than prophylactic doses as they are worried about undetected thrombi; however,





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this may lead to major bleeding events.[535] There are insufficient data to recommend increased anticoagulant doses for VTE prophylaxis in COVID-19 patients outside the setting of a clinical trial.[3] However, some guidelines recommend that escalated doses can be considered in critically ill patients.[532]

- Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected.[2]
- Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients.[3] [532] [533]
- There is little high-quality evidence for VTE prophylaxis in COVID-19 patients; therefore, clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[532]

Antimicrobials

- Consider empirical antibiotics if there is clinical suspicion of 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 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.[2] [3] [480]
- Some guidelines recommend empirical antibiotics for bacterial pathogens in all patients with community-acquired pneumonia without confirmed COVID-19. It is likely that the bacterial pathogens in patients with COVID-19 and pneumonia are the same as in previous patients with community-acquired pneumonia, and therefore empirical antimicrobial recommendations should be the same.[481] However, the National Institute for Health and Care Excellence (NICE) in the UK recommends that it is reasonable not to start empirical antimicrobials if you are confident that the clinical features are typical for COVID-19.[480] There is insufficient evidence to recommend empirical broad-spectrum antimicrobials in the absence of another indication.[3]
- Some patients may require continued antibiotic therapy once COVID-19 has been confirmed depending on the clinical circumstances (e.g., clinical or microbiological evidence of bacterial infection regardless of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] test results, SARS-CoV-2 test result is positive but clinical features are not typical for COVID-19). In these circumstances, review antibiotic choice based on microbiology results and switch to a narrower-spectrum antibiotic if appropriate, review intravenous antibiotic use within 48 hours and consider switching to oral therapy, and give for a total of 5 days unless there is a clear indication to continue.[480]
- Reassess antibiotic use daily. De-escalate empirical therapy on the basis of microbiology results and clinical judgement. 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 programmes should be in place.[2]
- Treat laboratory-confirmed co-infections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.[2]

Corticosteroids

- Consider low-dose dexamethasone for the management of hospitalised patients with COVID-19 who require oxygen or ventilation.
- Dexamethasone is associated with reduced mortality risk in patients with severe COVID-19 according to results from the RECOVERY trial in the UK. A total of 2104 patients were randomised



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to receive low-dose dexamethasone and were compared with 4321 patients randomised to usual care alone. Dexamethasone was found to reduce deaths by one third in patients who were ventilated, and by one fifth in patients who were receiving oxygen only. There were no excess harms identified in using this dose in this patient population. There was no benefit among patients who did not require respiratory support.[536]

- As a consequence of this trial, in the UK low-dose dexamethasone is now indicated for the treatment of suspected or confirmed COVID-19 in hospitalised adults receiving oxygen therapy, non-invasive or invasive ventilation, or extracorporeal membrane oxygenation. Oral prednisolone or intravenous hydrocortisone is recommended in pregnant or breastfeeding women. Use in children is still being studied.[502]
- In the US, the National Institutes of Health guideline panel recommends using dexamethasone in adults with COVID-19 who are mechanically ventilated, and in patients who require supplemental oxygen but who are not mechanically ventilated. The panel recommends against using dexamethasone in patients who do not require supplemental oxygen. It is unknown whether other corticosteroids have the same benefit. However, alternative corticosteroids (e.g., prednisolone, methylprednisolone, hydrocortisone) may be used in situations where dexamethasone is not available. Assess whether the patient is suitable for corticosteroid therapy before starting therapy.[3] The Infectious Diseases Society of America supports the use of dexamethasone in hospitalised patients with severe disease.[537]
- While the RECOVERY trial found significant benefit with the use of corticosteroids, results from retrospective studies are inconsistent and not strongly supportive of corticosteroid use in COVID-19 despite the signals for some benefits. More studies are necessary to substantiate conclusive benefit.[538] A living systematic review and network meta-analysis concluded that glucocorticoids probably reduce mortality and mechanical ventilation compared with standard care.[539]
- Monitor patients for adverse effects (e.g., hyperglycaemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions. The safety of coadministering dexamethasone and remdesivir is not known.[3]

Experimental therapies

- Consider experimental therapies such as remdesivir, hydroxychloroquine, lopinavir/ritonavir, and plasma therapy only in the context of a clinical trial or according to local protocols.[2]
- The certainty of the evidence for most interventions tested so far is low or very low; however, remdesivir, hydroxychloroquine, and lopinavir/ritonavir might reduce the time to symptom resolution. [BMJ: drug treatments for covid-19 – living systematic review and network meta-analysis]
- An expert guideline panel makes a weak recommendation for the use of remdesivir in severe disease, and supports more randomised trials as the quality of the evidence is low. [BMJ: remdesivir for severe covid-19 – a clinical practice guideline]
- See the Emerging section for more information.

Monitor

- Monitor patients closely for signs of clinical deterioration, and respond immediately with appropriate supportive care interventions.[2]

Discharge and rehabilitation




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- 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.[2]

## 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.[2]

Location of care

- Manage patients in an intensive/critical care unit under the guidance of a specialist team.[2]
- 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 pre-existing advanced comorbidities.[501]

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.[2]
- The CDC recommends discontinuing isolation once at least 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. In asymptomatic people, the CDC recommends discontinuing isolation once at least 20 days have passed since the date of a positive test. Alternatively, it 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 in these patients.[519]
- 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 hospitalised patients.[509]

Infection prevention and control

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

High-flow nasal oxygen or non-invasive ventilation

- Consider a trial of high-flow nasal oxygen (HFNO) or non-invasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in selected patients with mild acute respiratory distress syndrome (ARDS).[2]
- Airborne precautions are recommended for these interventions (including bubble CPAP) due to uncertainty about the potential for aerosolisation.[2] Novel methods to protect clinicians without access to standard personal protective equipment during aerosol-generating procedures have been suggested.[540] [541] [542] [543]



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- Patients with hypercapnia, haemodynamic 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 non-worsening hypercapnia. Patients with hypoxaemic respiratory failure and haemodynamic instability, multi-organ failure, or abnormal mental status should not receive these treatments in place of other options such as invasive ventilation.[2]
- There is ongoing debate about the optimal mode of respiratory support before mechanical ventilation.[544] NHS England recommends CPAP as the preferred form of non-invasive ventilation in patients with hypoxaemic (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.[545] Other guidelines recommend HFNO over non-invasive ventilation, unless HFNO is not available.[3] [510] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[546]
- 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).[545]
- Indirect and low-certainty evidence suggests that non-invasive ventilation probably reduces mortality in patients with COVID-19, similar to mechanical ventilation, but may increase the risk of viral transmission.[547]
- Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions, they require urgent endotracheal intubation.[2] [510]
- 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/non-invasive ventilatory support measures.[2] [3]
- Two-thirds of patients who required critical care in the UK had mechanical ventilation within 24 hours of admission.[548] In New York, 33% of hospitalised 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.[355] Patients spent an average of 18 days on a ventilator (range 9-28 days).[549]
- Endotracheal intubation should be performed by an experienced provider using airborne precautions.[2] Intubation by video laryngoscopy is recommended if possible.[3] Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require pre-oxygenation with 100% $FiO_2$ for 5 minutes.[2]
- 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, individualisation 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.[2] [3] [510] NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[550]
- 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 hypoxaemia.[551] [552] [553] [554] [555] [556] However, this approach has been criticised.[557] [558] It has been argued that an evidence-based approach extrapolating data from ARDS not related to COVID-19





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is the most reasonable approach for intensive care of COVID-19 patients.[559] 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 physiological findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.[551] PEEP should always be carefully titrated.[523]

- 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.[2] [3] [510] Longer durations may be feasible in some patients.[560] 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.[561] Two small case series found that many people tolerate the prone position while awake, breathing spontaneously, or receiving non-invasive ventilation. In the patients who tolerated it, improvement in oxygenation and a decrease in respiratory rate occurred.[562] [563]
- Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[3] [510]
- 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 hypoxaemia despite optimising ventilation. Taper off if there is no rapid improvement in oxygenation.[3] [510]

Extracorporeal membrane oxygenation

- Consider extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[2] [510] [564] [565] ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[566]
- There is insufficient evidence to recommend either for or against the routine use of ECMO.[3] Preliminary data on the use of ECMO in patients with COVID-19 was not promising.[567] [568] However, more recent data indicate that 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.[569]
- Single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure.[570]

Management of septic shock/sepsis

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

Symptom management and supportive care

- Consider fluid and electrolyte management, antimicrobial treatment, and experimental therapies as appropriate (see above).
- Manage symptoms such as fever, pain, cough, breathlessness, anxiety, agitation, delirium, depression, or insomnia as appropriate; mouth care is also important (see above).



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- VTE prophylaxis is recommended in critically ill patients. Low molecular weight heparin is the preferred option, with unfractionated heparin considered a suitable alternative and preferred over fondaparinux.[533]

Corticosteroids

- Consider low-dose dexamethasone for the management of hospitalised patients with COVID-19 who require oxygen or ventilation (see above).
- Surviving Sepsis Campaign guidelines suggest that adults with ARDS who are receiving mechanical ventilation and adults with refractory shock should receive corticosteroids, although this recommendation is based on weak evidence.[510]
- The overall pooled mortality rate from ARDS in COVID-19 patients is 39%; however, the median crude mortality rate in COVID-19 patients with reported corticosteroid use was 28%.[571]

Experimental therapies

- Consider experimental therapies (see above and the Emerging section).

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.[2]

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.[2] 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-centred, respectful, skilled approach to care is recommended.[2] In women with severe or critical disease, the multidisciplinary team should be organised as soon as possible after maternal hypoxaemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.[572] One in five pregnant women hospitalised with COVID-19 infection were admitted to the intensive care unit or required urgent delivery due to respiratory deterioration.[234]

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 physiological changes that occur with pregnancy.[2]

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).[573] [574] 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.[575] Another study




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in a New York obstetric population found that 88% of women who tested positive for SARS-CoV-2 at admission were asymptomatic at presentation.[576]

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.[2] Follow local infection prevention and control procedures as for non-pregnant people.
- Consider home care in women with asymptomatic or mild illness, provided the patient has no signs of potentially severe illness (e.g., breathlessness, haemoptysis, 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.[400] [577] [578]
- Postpone routine antenatal or postnatal health visits for women who are in home isolation and reschedule them after the isolation period is completed. Delivery of counselling 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.[2]
- The American College of Obstetricians and Gynecologists has published an algorithm to help decide whether hospital admission or home care is more appropriate. [ACOG: outpatient assessment and management for pregnant women with suspected or confirmed novel coronavirus (COVID-19)]

Antenatal corticosteroids

- Consider antenatal 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.[400] [578] [579] The World Health Organization (WHO) recommends antenatal 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.[2] Corticosteroids for fetal lung maturation have not been shown to cause more harm in patients with COVID-19.[580]

Labour and delivery

- Implement local infection prevention and control measures during labour and delivery. A negative pressure isolation room is recommended if available. Screen birth partners for COVID-19 infection using the standard case definition.[2]
- Individualise 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 labour, interventions to accelerate labour and delivery, and caesarean delivery are generally only recommended when medically justified based on maternal and fetal condition. COVID-19 positive status alone is not an indication for caesarean section.[2] [400] [578] Avoid using birthing pools in patients with suspected or confirmed infection.[580]
- 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



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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.[2]

- 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, if negative, again 48 hours after birth.[581]

Newborn care

- Experts are divided on separating mother and baby after delivery; make decisions on a case-by-base basis using shared-decision making.
- The World Health Organization (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).[2] The WHO advises that the benefits of breastfeeding outweigh the potential risks for transmission.[582]
- The Centers for Disease Control and Prevention 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 minimise the risk of transmission should be implemented.[583] A mother with confirmed infection should be counselled 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 carer.[584]
- The Royal College of Obstetricians and Gynaecologists (RCOG) recommends that mothers with confirmed infection and healthy babies are kept together in the immediate postnatal period. It is recommended that the risks and benefits are discussed with neonatologists and families in order to individualise 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.[580]
- The American Academy of Pediatrics (AAP) recommends that temporary separation is the safest option, but acknowledges there are situations where this is not possible or the mother chooses to room-in. The AAP supports breastfeeding as the best choice for feeding. Breast milk can be expressed after appropriate hygiene measures and fed by an uninfected carer. 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., distance, hand hygiene, respiratory hygiene/mask) for newborn care until either: they are afebrile for 72 hours without use of antipyretics and at least 10 days have passed since symptoms first appeared; or they have at least two consecutive negative SARS-CoV-2 tests from specimens collected ≥24 hours apart. This may require the support of an uninfected carer. A newborn with documented infection requires close outpatient follow-up after discharge for 14 days after birth.[581]

# Treatment details 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





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| Acute ( summary ) | | |
|---|---|---|
| **mild COVID-19** | | |
| | 1st | consider home isolation |
| | plus | monitoring |
| | plus | symptom management and supportive care |
| | adjunct | antipyretic/analgesic |
| **moderate COVID-19** | | |
| | 1st | consider home isolation or hospital admission |
| | plus | monitoring |
| | plus | symptom management and supportive care |
| | adjunct | antibiotics |
| | adjunct | antipyretic/analgesic |
| **severe COVID-19** | | |
| | 1st | hospital admission |
| | plus | consider oxygen therapy |
| | plus | symptom management and supportive care |
| | plus | venous thromboembolism prophylaxis |
| | plus | monitoring |
| | plus | consider antibiotics |
| | adjunct | corticosteroid |
| | adjunct | treatment of co-infections |
| | adjunct | antipyretic/analgesic |
| | adjunct | experimental therapies |
| | adjunct | plan for discharge and rehabilitation |
| **critical COVID-19** | | |
| | 1st | intensive/critical care unit admission |
| | plus | symptom management and supportive care |
| | plus | consider high-flow nasal oxygen or non-invasive ventilation |
| | plus | consider invasive mechanical ventilation |



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| Acute | | ( summary ) |
|---|---|---|
| | adjunct | inhaled pulmonary vasodilator |
| | adjunct | extracorporeal membrane oxygenation |
| | adjunct | management of sepsis/septic shock |
| | adjunct | corticosteroid |
| | adjunct | experimental therapies |
| | adjunct | plan for discharge and rehabilitation |
| | adjunct | palliative care |





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# Treatment options

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# Acute

## mild COVID-19

**1st** **consider home isolation**

» 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.[2]

» 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.[2] [3] This decision requires careful clinical judgement 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 carer is able to provide care and recognise when the patient may be deteriorating; the carer has adequate support (e.g., food, supplies, psychological support); the support of a trained health worker is available in the community.[495] 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.[2]

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

» [WHO: home care for patients with suspected or confirmed COVID-19 and management of their contacts]

» [CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19)]

» 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).[2] The US Centers for Disease Control and Prevention (CDC) recommends discontinuing home isolation once at least 10 days have passed since symptoms first





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## Acute

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. Alternatively, it 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.[508] If the patient is hospitalised, 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.[509]

**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).[2] [3]

**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 (e.g., a teaspoon of honey in patients aged 1 year and older) to help cough.[501] 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.[517]

» Advise patients about adequate nutrition and appropriate rehydration. Too much fluid can worsen oxygenation.[2]

» Advise patients to improve air circulation by opening a window or door (fans can spread infection and should not be used).[501]

» Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[2]



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## Acute

» 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.[518]

**adjunct** **antipyretic/analgesic**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» paracetamol: children: consult local drug formulary for guidance on dose; adults: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

**OR**

» ibuprofen: children: consult local drug formulary for guidance on dose; adults: 300-600 mg orally (immediate-release) every 6-8 hours when required, maximum 2400 mg/day

» Paracetamol or ibuprofen are recommended.[2] [510] There is no evidence at present of severe adverse events in COVID-19 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[2] [501] [511] [512] [513] [514] [515] [516]

» 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).

### 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.[2]

» 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.[2] [3]





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## Acute

» 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:

» [WHO: home care for patients with suspected or confirmed COVID-19 and management of their contacts]

» [CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19)]

» 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.[2] [519] The US Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 10 days (not severely immunocompromised) or 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 20 days (severely immunocompromised) have passed since the date of a positive test. Alternatively, it 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 in these patients.[519] 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 hospitalised patients, and 10 days in patients with milder disease who are managed in the community.[509]

**plus** **monitoring**

Treatment recommended for ALL patients in selected patient group

» Closely monitor patients for signs or symptoms of disease progression. If the patient is being managed at home, counsel them about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty



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breathing, chest pain). 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.[2]

**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 (e.g., a teaspoon of honey in patients aged 1 year and older) to help cough.[501] 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.[517]

» Advise patients about adequate nutrition and appropriate rehydration. Too much fluid can worsen oxygenation.[2]

» Advise patients to improve air circulation by opening a window or door (fans can spread infection and should not be used).[501]

» Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[2]

» 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.[518]

**adjunct** **antibiotics**

Treatment recommended for SOME patients in selected patient group

» Consider empirical antibiotics if there is clinical suspicion of bacterial infection.[2] [3] Antibiotics may also be considered in older people (particularly those in long-term care facilities) and children <5 years of age to provide empirical antibiotic treatment for possible pneumonia. The regimen should be based on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.[2]

**adjunct** **antipyretic/analgesic**





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Treatment recommended for SOME patients in selected patient group

**Primary options**

» paracetamol: children: consult local drug formulary for guidance on dose; adults: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

**OR**

» ibuprofen: children: consult local drug formulary for guidance on dose; adults: 300-600 mg orally (immediate-release) every 6-8 hours when required, maximum 2400 mg/day

» Paracetamol or ibuprofen are recommended.[2] [510] There is no evidence at present of severe adverse events in COVID-19 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[2] [501] [511] [512] [513] [514] [515] [516]

» 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).

### 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 $SpO_2$ <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 $SpO_2$ <90%, severe respiratory distress, general danger sign, inability to breastfeed or drink, lethargy or unconsciousness, or convulsions).[2]

» Assess all adults for frailty on admission to hospital, irrespective of age and COVID-19 status, using the Clinical Frailty Scale (CFS).



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[Clinical frailty scale] Involve critical care teams in discussions about admission to critical care.[500] A large observational study found that disease outcomes were better predicted by frailty than either age or comorbidity; frailty (CFS score 5-8) was associated with earlier death and longer duration of hospital stay, and these outcomes worsened with increasing frailty after adjustment for age and comorbidity.[520]

» 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-centred, respectful, skilled approach to care is recommended.[2] The multidisciplinary team should be organised as soon as possible after maternal hypoxemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.[572]

» 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.[2] The US Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 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. In asymptomatic people, the CDC recommends discontinuing isolation once at least 20 days have passed since the date of a positive test. Alternatively, it 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 in these patients.[519] 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 hospitalised patients.[509]

**plus** **consider oxygen therapy**

Treatment recommended for ALL patients in selected patient group

» Start supplemental oxygen therapy immediately in any patient with emergency signs

TREATMENT



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(i.e., obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions), or any patient without emergency signs and $SpO_2$ <90%.[2] [3]

» Target $SpO_2$ to ≥94% during resuscitation in adults and children with emergency signs who require emergency airway management and oxygen therapy. Once the patient is stable, a target $SpO_2$ >90% in children and non-pregnant adults, and ≥92% to 95% in pregnant women, is recommended. Nasal prongs or a nasal cannula are preferred in young children.[2] Some guidelines recommend that $SpO_2$ should be maintained no higher than 96%.[510]

» Some centres may recommend different $SpO_2$ targets in order to support prioritisation of oxygen flow for the most severely ill patients in hospital. NHS England recommends a target of 92% to 95% (or 90% to 94% if clinically appropriate), for example.[522]

» Consider positioning techniques (e.g., high supported sitting, prone position), and airway clearance management to assist with secretion clearance in adults.[2] Oxygen delivery can be increased by using a non-rebreathing mask and prone positioning.[523] Consider a trial of awake prone positioning to improve oxygenation in patients with persistent hypoxaemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated.[3] Early self-proning of awake, non-intubated patients has been shown to improve oxygen saturation and may delay or reduce the need for intensive care.[524] [525] [526] [527] [528]

» Monitor patients closely for signs of progressive acute hypoxaemic respiratory failure.[2] [3]

**plus** **symptom management and supportive care**

Treatment recommended for ALL patients in selected patient group

» Fluids and electrolytes: use cautious fluid management in adults and children without tissue hypoperfusion and fluid responsiveness as aggressive fluid resuscitation may worsen oxygenation.[2] Correct any electrolyte or metabolic abnormalities, such as hyperglycaemia or metabolic acidosis, according to local protocols.[529]



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» Cough: advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures (e.g., a teaspoon of honey in patients aged 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.[501] 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.[517]

» 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 oedema). Consider a trial of oxygen, if available. Consider an opioid and benzodiazepine combination in patients with moderate to severe breathlessness or patients who are distressed.[501]

» Anxiety, delirium, and agitation: identify and treat any underlying or reversible causes (e.g., offer reassurance, treat hypoxia, correct metabolic or endocrine abnormalities, address co-infections, minimise use of drugs that may cause or worsen delirium, treat substance withdrawal, maintain normal sleep cycles, treat pain or breathlessness).[2] [501] Consider a benzodiazepine for the management of anxiety or agitation that does not respond to other measures. Consider haloperidol or a phenothiazine for the management of delirium.[501] Low doses of haloperidol (or another suitable antipsychotic) can also be considered for agitation.[2] Non-pharmacological interventions are the mainstay for the management of delirium when possible, and prevention is key.[530]

» Mouth care: an important part of overall patient care in hospitalised patients who are ventilated or non-ventilated and those undergoing step-down or end-of-life care.[531]

» Mental health symptoms: provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[2]

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

Treatment recommended for ALL patients in selected patient group

### Primary options

TREATMENT



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## Acute

» enoxaparin: consult specialist for guidance on dose

**OR**

» dalteparin: consult specialist for guidance on dose

**OR**

» fondaparinux: consult specialist for guidance on dose

### Secondary options

» heparin: consult specialist for guidance on dose

» Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalised adults and adolescents with COVID-19 as per the standard of care for other hospitalised patients without COVID-19, provided there are no contraindications. A COVID-19 diagnosis should not influence a paediatrician's recommendations about VTE prophylaxis in hospitalised children. Pregnant women should be managed by a specialist.[2] [3] [532] [533]

» Low molecular weight heparin or fondaparinux are preferred over unfractionated heparin in order to reduce patient contact. Unfractionated heparin is contraindicated in patients with severe thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia. Direct oral anticoagulants are not recommended. Mechanical thromboprophylaxis (e.g., intermittent pneumatic compression devices) is recommended if anticoagulation is contraindicated or not available.[2] [533] [534]

» The optimal dose is unknown. Standard prophylaxis doses are recommended over intermediate- or full treatment-dose regimens.[533] Some clinicians are using intermediate- or full treatment-dose regimens rather than prophylactic doses as they are worried about undetected thrombi; however, this may lead to major bleeding events.[535] There are insufficient data to recommend increased anticoagulant doses for VTE prophylaxis in COVID-19 patients outside the setting of a clinical trial.[3] However, some guidelines recommend that escalated doses can be considered in critically ill patients.[532]



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» Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected.[2]

» Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients.[3] [532] [533]

» There is little high-quality evidence for VTE prophylaxis in COVID-19 patients; therefore, clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[532]

**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.[2]

**plus** **consider antibiotics**

Treatment recommended for ALL patients in selected patient group

» Consider empirical antibiotics if there is clinical suspicion of 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 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.[2] [3] [480]

» Some guidelines recommend empirical antibiotics for bacterial pathogens in all patients with community-acquired pneumonia without confirmed COVID-19. It is likely that the bacterial pathogens in patients with COVID-19 and pneumonia are the same as in previous patients with community-acquired pneumonia, and therefore empirical antimicrobial recommendations should be the same.[481] However, the National Institute for Health and Care Excellence in the UK recommends that it is reasonable not to start empirical antimicrobials if you are confident that the clinical features are typical for COVID-19.[480] There is insufficient evidence to recommend empirical broad-spectrum antimicrobials in the absence of another indication.[3]





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» Some patients may require continued antibiotic therapy once COVID-19 has been confirmed depending on the clinical circumstances (e.g., clinical or microbiological evidence of bacterial infection regardless of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] test results, SARS-CoV-2 test result is positive but clinical features are not typical for COVID-19). In these circumstances, review antibiotic choice based on microbiology results and switch to a narrower-spectrum antibiotic if appropriate, review intravenous antibiotic use within 48 hours and consider switching to oral therapy, and give for a total of 5 days unless there is a clear indication to continue.[480]

» Reassess antibiotic use daily. De-escalate empirical therapy on the basis of microbiology results and clinical judgement. 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 programmes should be in place.[2]

**adjunct** **corticosteroid**

Treatment recommended for SOME patients in selected patient group

### Primary options

» dexamethasone: 6 mg orally/intravenously once daily for 10 days

### Secondary options

» prednisolone: 40 mg/day orally given in 1-2 divided doses for 10 days

**OR**

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

**OR**

» hydrocortisone: 160 mg/day orally/intravenously given in 2-4 divided doses for 10 days

» Consider low-dose dexamethasone for the management of hospitalised patients with COVID-19 who require oxygen or ventilation. Dexamethasone is associated with reduced mortality risk in patients with severe COVID-19 according to results from the RECOVERY trial in the UK. A total of 2104



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patients were randomised to receive low-dose dexamethasone and were compared with 4321 patients randomised to usual care alone. Dexamethasone was found to reduce deaths by one third in patients who were ventilated, and by one fifth in patients who were receiving oxygen only. There were no excess harms identified in using this dose in this patient population. There was no benefit among patients who did not require respiratory support.[536]

» As a consequence of this trial, in the UK low-dose dexamethasone is now indicated for the treatment of suspected or confirmed COVID-19 in hospitalised adults receiving oxygen therapy, non-invasive or invasive ventilation, or extracorporeal membrane oxygenation. Oral prednisolone or intravenous hydrocortisone is recommended in pregnant or breastfeeding women. Use in children is still being studied.[502]

» In the US, the National Institutes of Health guideline panel recommends using dexamethasone in adults with COVID-19 who are mechanically ventilated, and in patients who require supplemental oxygen but who are not mechanically ventilated. The panel recommends against using dexamethasone in patients who do not require supplemental oxygen. It is unknown whether other corticosteroids have the same benefit. However, alternative corticosteroids (e.g., prednisolone, methylprednisolone, hydrocortisone) may be used in situations where dexamethasone is not available. Assess whether the patient is suitable for corticosteroid therapy before starting therapy.[3] The Infectious Diseases Society of America supports the use of dexamethasone in hospitalised patients with severe disease.[537]

» While the RECOVERY trial found significant benefit with the use of corticosteroids, results from retrospective studies are inconsistent and not strongly supportive of corticosteroid use in COVID-19 despite the signals for some benefits. More studies are necessary to substantiate conclusive benefit.[538]

» Monitor patients for adverse effects (e.g., hyperglycaemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions. The safety of coadministering dexamethasone and remdesivir is not known.[3]

**adjunct** **treatment of co-infections**





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Treatment recommended for SOME patients in selected patient group

» Treat laboratory-confirmed co-infections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.[2]

**adjunct** **antipyretic/analgesic**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» paracetamol: children: consult local drug formulary for guidance on dose; adults: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

**OR**

» ibuprofen: children: consult local drug formulary for guidance on dose; adults: 300-600 mg orally (immediate-release) every 6-8 hours when required, maximum 2400 mg/day

» Paracetamol or ibuprofen are recommended.[2] [510] There is no evidence at present of severe adverse events in COVID-19 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[2] [501] [511] [512] [513] [514] [515] [516]

» 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 experimental therapies such as remdesivir, hydroxychloroquine, lopinavir/ritonavir, and plasma therapy only in the context of a clinical trial or according to local protocols.[2]

» The certainty of the evidence for most interventions tested so far is low or very low; however, remdesivir, hydroxychloroquine, and lopinavir/ritonavir might reduce the time to symptom resolution. [BMJ: drug treatments for



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covid-19 – living systematic review and network meta-analysis]

» An expert guideline panel makes a weak recommendation for the use of remdesivir in severe disease, and supports more randomised trials as the quality of the evidence is low. [BMJ: remdesivir for severe covid-19 – a clinical practice guideline]

» 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.[2]

### 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.[2]

» 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 pre-existing advanced comorbidities.[501]

» 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-centred, respectful, skilled approach to care is recommended.[2] The multidisciplinary team should be organised as soon as possible after maternal hypoxemia occurs in order to assess





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fetal maturity, disease progression, and the best options for delivery.[572]

» 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.[2] The US Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 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. In asymptomatic people, the CDC recommends discontinuing isolation once at least 20 days have passed since the date of a positive test. Alternatively, it 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 in these patients.[519] 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 hospitalised patients.[509]

**plus** **symptom management and supportive care**

Treatment recommended for ALL patients in selected patient group

» Consider fluid and electrolyte management, and antimicrobial treatment. Manage symptoms such as fever, pain, cough, breathlessness, anxiety, agitation, delirium, depression, or insomnia as appropriate. Mouth care is also important. Venous thromboembolism prophylaxis is recommended in critically ill patients. Low molecular weight heparin is the preferred option, with unfractionated heparin considered a suitable alternative and preferred over fondaparinux.[533] See Severe COVID-19 section above for more detailed information.

» Implement standard interventions to prevent complications associated with critical illness.[2]

**plus** **consider high-flow nasal oxygen or non-invasive ventilation**

Treatment recommended for ALL patients in selected patient group

» Consider a trial of high-flow nasal oxygen (HFNO) or non-invasive ventilation (e.g., continuous positive airway pressure [CPAP]



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or bilevel positive airway pressure [BiPAP]) in selected patients with mild acute respiratory distress syndrome.[2]

» Airborne precautions are recommended for these interventions (including bubble CPAP) due to uncertainty about the potential for aerosolisation.[2]

» Patients with hypercapnia, haemodynamic 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 non-worsening hypercapnia. Patients with hypoxaemic respiratory failure and haemodynamic instability, multi-organ failure, or abnormal mental status should not receive these treatments in place of other options such as invasive ventilation.[2]

» There is ongoing debate about the optimal mode of respiratory support before mechanical ventilation.[544] NHS England recommends CPAP as the preferred form of non-invasive ventilation in patients with hypoxaemic (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.[545] Other guidelines recommend HFNO over non-invasive ventilation, unless HFNO is not available.[3] [510] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[546]

» 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).[545]

» Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions, they require urgent endotracheal intubation.[2] [510]

**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/ non-invasive ventilatory support measures.[2] [3]





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» Endotracheal intubation should be performed by an experienced provider using airborne precautions.[2] Intubation by video laryngoscopy is recommended if possible.[3] Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require pre-oxygenation with 100% fraction of inspired oxygen ($FiO_2$) for 5 minutes.[2]

» 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, individualisation 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.[2] [3] [510] NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[550]

» 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 hypoxaemia.[551] [552] [553] [554] [555] [556] However, this approach has been criticised.[557] [558] 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.[559] 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 physiological findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.[551] PEEP should always be carefully titrated.[523]

» 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.[2] [3]



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[510] Longer durations may be feasible in some patients.[560]

» Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[3] [510]

**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 hypoxaemia despite optimising ventilation. Taper off if there is no rapid improvement in oxygenation.[3] [510]

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

Treatment recommended for SOME patients in selected patient group

» Consider extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[2] [510] [564] [565] ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[566]

» There is insufficient evidence to recommend either for or against the routine use of ECMO.[3] Preliminary data on the use of ECMO in patients with COVID-19 was not promising.[567] [568] However, more recent data indicate that 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.[569]

» Single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure.[570]

**adjunct** **management of sepsis/septic shock**

Treatment recommended for SOME patients in selected patient group

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

**adjunct** **corticosteroid**

Treatment recommended for SOME patients in selected patient group

### Primary options

» dexamethasone: 6 mg orally/intravenously once daily for 10 days





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# Acute

### Secondary options

» prednisolone: 40 mg/day orally given in 1-2 divided doses for 10 days

**OR**

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

**OR**

» hydrocortisone: 160 mg/day orally/ intravenously given in 2-4 divided doses for 10 days

» Consider low-dose dexamethasone for the management of hospitalised patients with COVID-19 who require oxygen or ventilation. Dexamethasone is associated with reduced mortality risk in patients with severe COVID-19 according to results from the RECOVERY trial in the UK. A total of 2104 patients were randomised to receive low-dose dexamethasone and were compared with 4321 patients randomised to usual care alone. Dexamethasone was found to reduce deaths by one third in patients who were ventilated, and by one fifth in patients who were receiving oxygen only. There were no excess harms identified in using this dose in this patient population. There was no benefit among patients who did not require respiratory support.[536]

» As a consequence of this trial, in the UK low-dose dexamethasone is now indicated for the treatment of suspected or confirmed COVID-19 in hospitalised adults receiving oxygen therapy, non-invasive or invasive ventilation, or extracorporeal membrane oxygenation. Oral prednisolone or intravenous hydrocortisone is recommended in pregnant or breastfeeding women. Use in children is still being studied.[502]

» In the US, the National Institutes of Health guideline panel recommends using dexamethasone in adults with COVID-19 who are mechanically ventilated, and in patients who require supplemental oxygen but who are not mechanically ventilated. The panel recommends against using dexamethasone in patients who do not require supplemental oxygen. It is unknown whether other corticosteroids have the same benefit. However, alternative corticosteroids



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## Acute

(e.g., prednisolone, methylprednisolone, hydrocortisone) may be used in situations where dexamethasone is not available. Assess whether the patient is suitable for corticosteroid therapy before starting therapy.[3] The Infectious Diseases Society of America supports the use of dexamethasone in hospitalised patients with severe disease.[537]

» While the RECOVERY trial found significant benefit with the use of corticosteroids, results from retrospective studies are inconsistent and not strongly supportive of corticosteroid use in COVID-19 despite the signals for some benefits. More studies are necessary to substantiate conclusive benefit.[538]

» Surviving Sepsis Campaign guidelines suggest that adults with acute respiratory distress syndrome who are receiving mechanical ventilation and adults with refractory shock should receive corticosteroids, although this recommendation is based on weak evidence.[510]

» Monitor patients for adverse effects (e.g., hyperglycaemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions. The safety of coadministering dexamethasone and remdesivir is not known.[3]

**adjunct** **experimental therapies**

Treatment recommended for SOME patients in selected patient group

» Consider experimental therapies such as remdesivir, hydroxychloroquine, lopinavir/ritonavir, and plasma therapy only in the context of a clinical trial or according to local protocols.[2]

» The certainty of the evidence for most interventions tested so far is low or very low; however, remdesivir, hydroxychloroquine, and lopinavir/ritonavir might reduce the time to symptom resolution. [BMJ: drug treatments for covid-19 – living systematic review and network meta-analysis]

» An expert guideline panel makes a weak recommendation for the use of remdesivir in severe disease, and supports more randomised trials as the quality of the evidence is low. [BMJ: remdesivir for severe covid-19 – a clinical practice guideline]





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## 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 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.[2]

**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.[2] Follow local palliative care guidelines.



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# Emerging

## Introduction

Various treatments for COVID-19 are in clinical trials around the world. [Global coronavirus COVID-19 clinical trial tracker] No treatments have been approved or shown to be safe and effective for the treatment of COVID-19, with the exception of remdesivir, which has been granted an emergency-use authorisation in the US. There are several treatments being used off-label (use of a licensed medication for an indication that has not been approved by a national drug regulatory authority), on a compassionate-use basis, or as part of a randomised controlled trial.[585] [586] [WHO: off-label use of medicines for COVID-19] It is important to note that there may be serious adverse effects associated with these drugs, and that these adverse effects may overlap with the clinical manifestations of COVID-19. These drugs may also increase the risk of death in an older patient or a patient with an underlying health condition. For example, chloroquine/hydroxychloroquine, azithromycin, oseltamivir, and lopinavir/ritonavir can all prolong the QT interval and are all potentially associated with an increased risk of cardiac death.[587] Drug-drug interactions with the patient's existing medication(s) must also be considered (e.g., antivirals can interact with many drugs including direct oral anticoagulants). The World Health Organization (WHO) and its partners have launched the Solidarity trial, a large international study to compare four different treatments (local standard of care plus remdesivir, lopinavir/ritonavir, lopinavir/ritonavir plus interferon beta, or hydroxychloroquine/chloroquine) compared with local standard of care alone (which may include other experimental drug therapies as part of local standard of care).[588] A national trial to identify treatments that may be beneficial for people hospitalised with suspected or confirmed COVID-19 is ongoing in the UK. The randomised evaluation of COVID-19 therapy (RECOVERY) trial is testing the following therapeutic options: lopinavir/ritonavir; low-dose dexamethasone; hydroxychloroquine; azithromycin; tociluzumab; and convalescent plasma. [RECOVERY trial]

## Remdesivir

A novel intravenous nucleoside analogue with broad antiviral activity that shows in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In the US, the Food and Drug Administration (FDA) has issued an emergency-use authorisation for remdesivir for the treatment of suspected or confirmed COVID-19 in adults and children with hospitalised severe disease (defined as patients with low blood oxygen levels or needing oxygen therapy or more intensive breathing support such as a mechanical ventilator).[589] This authorisation is based on preliminary results from a randomised, placebo-controlled trial of remdesivir in 1063 patients hospitalised with severe COVID-19 run by the National Institute of Allergy and Infectious Disease (NIAID). The study found that patients taking a 10-day course of remdesivir had a faster time to recovery (i.e., defined as a patient no longer requiring hospitalisation, or hospitalisation no longer requiring oxygen or ongoing medical care) compared with placebo, with a median recovery time of 11 days versus 15 days. Results were significant only among patients who received oxygen. The mortality rate was 7.1% with remdesivir compared with 11.9% with placebo, although the difference was not statistically significant. The incidence of adverse effects was not significantly different between the two groups. Even though the trial was ongoing, the data and safety monitoring board made the recommendation to unblind the results to the trial team members from NIAID, who subsequently decided to make the results public.[590] The National Institutes of Health guidelines recommend prioritising remdesivir in hospitalised patients with COVID-19 who require supplemental oxygen, but who are not on high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation. The guidelines panel recommends that patients should receive treatment for 5 days or until hospital discharge, whichever comes first (patients who have not shown clinical improvement after 5 days can receive treatment for up to 10 days). The guidelines panel does not recommend for or against remdesivir for the treatment of mild or moderate COVID-19, or patients with more severe disease who require high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation, as there are insufficient data.[3] The Infectious Diseases Society of America recommends remdesivir over no antiviral treatment among hospitalised patients with severe COVID-19, with the same treatment duration as recommended above.[537] A UK National Institute for Health and Care Excellence review suggests there is some benefit with remdesivir compared with placebo for reducing supportive measures including mechanical ventilation and reducing time to recovery in patients with mild, moderate, or severe COVID-19 who are on oxygen therapy. However, no statistically significant differences were found for mortality and serious adverse events.[591] An expert guideline panel makes a weak recommendation for the use of remdesivir in severe disease, and supports




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more randomised trials as the quality of the evidence is low. [BMJ: remdesivir for severe covid-19 – a clinical practice guideline] A network meta-analysis found that both 5-day and 10-day remdesivir regimens were associated with higher odds of clinical improvement in hospitalised patients compared with placebo.[592] Remdesivir appears to be safe to use in pregnancy.[593] Possible adverse effects include elevated liver enzymes and infusion-related reactions (e.g., hypotension, nausea, vomiting, sweating, shivering). The FDA recommends against the concomitant use of remdesivir with chloroquine or hydroxychloroquine due to a drug interaction that may result in reduced antiviral activity of remdesivir, although this has not been observed in practice.[594] The European Medicines Agency has recommended granting a conditional marketing authorisation to remdesivir for the treatment of COVID-19 in adults and children 12 years of age and older with pneumonia who require supplemental oxygen.[595] An interim clinical commissioning policy has been put in place to define routine access to remdesivir in the treatment of COVID-19 across the UK from 3 July.[596] Clinical trials of inhaled remdesivir, and remdesivir plus interferon beta-1a, have started.[597]

## Hydroxychloroquine/chloroquine

Hydroxychloroquine and chloroquine are oral drugs that have been used for the prophylaxis and treatment of malaria, and the treatment of certain autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus. Both drugs have in vitro activity against SARS-CoV-2, with hydroxychloroquine having relatively higher potency.[598] [599] They are being trialled in patients for the treatment and prophylaxis of COVID-19; however, most ongoing trials use hydroxychloroquine instead of chloroquine. Initial data seemed promising, but evidence so far is weak and conflicting.[600] A small randomised controlled trial found that hydroxychloroquine (with or without azithromycin) was efficient in reducing viral nasopharyngeal carriage of SARS-CoV-2 in 3 to 6 days in most patients.[601] However, this trial has been criticised for its limitations, and results from a similar trial could not replicate these findings.[602] [603] Another randomised trial in 62 patients in China found that hydroxychloroquine may shorten time to clinical recovery (in terms of resolution of fever and cough, and improvement of pneumonia on computed tomographic imaging); however, this study has not been peer reviewed as yet.[604] Early results from a randomised controlled trial of 150 people in China found that the overall 28-day negative conversion rate was not significantly different between patients who received hydroxychloroquine and those who received standard of care. However, addition of hydroxychloroquine led to more rapid normalisation of C-reactive protein levels and recovery of baseline lymphopenia, which may be important. The time to the alleviation of symptoms was shorter compared with standard of care in the subgroup of patients who did not receive antiviral treatment in the post-hoc analysis. The rate of adverse effects was higher in the hydroxychloroquine group (diarrhoea being the most common adverse effect). This study has not been peer reviewed yet and has several limitations (e.g., delay between symptom onset and starting treatment, inclusion of other antiviral therapies in the standard of care group).[605] According to an observational study of over 1400 hospitalised patients in New York, hydroxychloroquine was not associated with a reduced risk for intubation or death compared with those who did not receive hydroxychloroquine, and the authors conclude that further randomised controlled trials are needed.[606] Another observational study of 181 patients across four tertiary care centres in France found that in patients with severe COVID-19 who require oxygen, hydroxychloroquine appeared to have no effect on reducing admissions to intensive care or deaths at day 21 after hospital admission.[607] A multinational registry analysis of the use of hydroxychloroquine or chloroquine (with or without a macrolide antibiotic) found that the use of these regimens was independently associated with an increased risk of in-hospital mortality and ventricular arrhythmias; however, the study has now been retracted.[608] The study was criticised by more than 140 scientists and physicians in an open letter to the authors that lists numerous concerns about the validity of the study.[609] [610] Preliminary results from the UK RECOVERY trial found that hydroxychloroquine does not reduce the risk of dying or improve other outcomes in hospitalised patients, and investigators have stopped enrolling participants into the hydroxychloroquine arm of the trial.[611] As a consequence of this, the WHO stopped the hydroxychloroquine arm of the Solidarity trial on 17 June.[612] A randomised, double-blind, placebo-controlled trial found that hydroxychloroquine did not prevent symptomatic infection when used as postexposure prophylaxis within 4 days of moderate- or high-risk exposure; however, the vast majority of participants were not able to access testing and the outcome was based on the presence of symptoms compatible with COVID-19 rather than a confirmed positive test result with molecular testing.[613] Despite these negative results, recently a multicentre retrospective observational study of over 2500 patients in the US found that treatment with hydroxychloroquine alone (and in combination with azithromycin) was associated with a reduction in mortality when controlling for risk factors.[614] A 5-day course of hydroxychloroquine did not substantially reduce symptom severity in outpatients with probable or confirmed early mild COVID-19 in a randomised, double-blind, placebo-controlled trial of nearly 500 people; however, only 58% of participants received SARS-CoV-2 testing.[615]



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An open-label randomised controlled trial of patients with mild to moderate disease found that a 7-day course of hydroxychloroquine (either with azithromycin or alone) did not result in better clinical outcomes as measured by a seven-level ordinal scale at 15 days compared with standard care, although the trial had several limitations.[616] Hydroxychloroquine has similar therapeutic effects to chloroquine, but fewer adverse effects, is considered safe in pregnancy, and is more readily available in some countries.[617] Both drugs must be used with caution in patients with pre-existing cardiovascular disease due to the risk of arrhythmias.[618] It is reasonable to do a baseline echocardiogram before treatment whenever possible, particularly in patients who are critically ill.[619] Higher doses of chloroquine have been associated with an increased risk of QT interval prolongation compared with lower doses, especially when used in combination with other drugs that prolong the QT interval.[620] Because chloroquine/hydroxychloroquine and azithromycin can both cause QT interval prolongation, caution is recommended when using these drugs together.[621] [622] The risk of QT interval prolongation and/or ventricular tachycardia (including Torsades de Pointes) is greater when these drugs are used in combination compared with the risk associated with either drug used alone (0.6% versus 1.5%).[623] A preprint study (not peer reviewed) found an increased risk of 30-day cardiovascular mortality when azithromycin was added to hydroxychloroquine in patients with COVID-19.[624] This combination is not recommended except in the context of a clinical trial.[3] [537] Caution is recommended with the dosing regimen used for chloroquine due to the risk of chloroquine poisoning.[625] Guidelines in China and Italy recommend these drugs for the treatment of COVID-19; however, this is based on weak evidence.[626] Surviving Sepsis Campaign and National Institutes of Health guidelines concluded that there is insufficient evidence to offer any recommendation on use of these drugs in the intensive care unit.[510] The National Institutes of Health recommends against the use of either drug except in a clinical trial, but has stopped its clinical trials.[3] The Infectious Diseases Society of America recommends these drugs only in the context of a clinical trial.[537] The American Thoracic Society recommends that either drug may be used on a case-by-case basis provided the patient's condition is severe enough to warrant investigational therapy, the benefits and risks of treatment are discussed with the patient, data is collected on outcomes, and the drug is not in short supply.[564] The European Medicines Agency (EMA) has stressed that these drugs have not been shown to be effective in treating COVID-19 as yet, and should only be used in the context of clinical trials or emergency-use programmes.[627] Based on results from the RECOVERY trial, the UK Medicines and Healthcare products Regulatory Agency has instructed researchers in the UK who are using hydroxychloroquine in clinical trials to suspend recruitment of further participants, although hydroxychloroquine will still be able to be used in trials for the prevention of COVID-19 in healthcare workers.[628] In the US, the FDA has revoked its emergency-use authorisation for chloroquine and hydroxychloroquine as it believes the potential benefits no longer outweigh the known and potential risks.[629] It recommends that these drugs should not be used outside of the hospital setting or a clinical trial due to the risk of arrhythmias, especially when used in combination with azithromycin.[630] There is currently no strong evidence of efficacy of hydroxychloroquine or chloroquine in the treatment or prevention of COVID-19.[631] [Centre for Evidence-Based Medicine: hydroxychloroquine for COVID-19 – what do the clinical trials tell us?]

## Lopinavir/ritonavir

An oral antiretroviral protease inhibitor currently approved for the treatment of HIV Infection. Lopinavir/ritonavir has been used in clinical trials for the treatment of COVID-19. Results from one small case series found that evidence of clinical benefit with lopinavir/ritonavir was equivocal.[632] A randomised controlled trial of 200 patients with severe disease found that treatment with lopinavir/ritonavir plus standard care (i.e., oxygen, non-invasive and invasive ventilation, antibiotics, vasopressors, renal replacement therapy, and extracorporeal membrane oxygenation, as necessary) was not associated with an decreased time to clinical improvement compared with standard care alone, and 28-day mortality was similar in both groups.[633] Preliminary results from the UK RECOVERY trial found that there is no beneficial effect of lopinavir/ritonavir in hospitalised patients with COVID-19. There was no significant difference in 28-day mortality, risk of progression to mechanical ventilation, or duration of hospital stay between the two treatment arms (lopinavir/ritonavir versus usual care alone), and the results were consistent in different subgroups of patients.[634] Lopinavir/ritonavir may increase the risk of bradycardia, especially in older, critically ill patients.[635] Lopinavir/ritonavir should only be used in the context of a clinical trial.[3] [Centre for Evidence-Based Medicine: lopinavir/ritonavir – a rapid review of effectiveness in COVID-19]

## Convalescent plasma




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Convalescent plasma from patients who have recovered from viral infections has been used as a treatment in previous virus outbreaks including SARS, avian influenza, and Ebola virus infection.[636] Clinical trials to determine the safety and efficacy of convalescent plasma that contains antibodies to SARS-CoV-2 in patients with COVID-19 are ongoing. A randomised controlled trial found that convalescent plasma added to standard treatment did not significantly improve time to clinical improvement within 28 days in patients with severe or life-threatening disease. However, the trial was terminated early and may have been underpowered to detect a clinically important difference.[637] A systematic review of five studies found that convalescent plasma may reduce mortality in critically ill patients, have a beneficial effect on clinical symptoms, and reduce viral load.[638] A meta-analysis and systematic review with a total of 5444 patients found that the use of convalescent plasma reduced mortality, increased viral clearance, and resulted in clinical improvement in patients with COVID-19; however, the evidence is of low quality and further randomised controlled trials are required.[639] A preprint (not peer reviewed) of an open-label, multicentre, expanded access programme study of over 35,000 patients suggested that convalescent plasma lowered mortality in hospitalised patients when given within 3 days of diagnosis; however, there was no placebo group in this trial.[640] In the US, the FDA has classified convalescent plasma as an investigational product (available via clinical trials, an expanded access programme, or a single-patient emergency investigational new drug application), and has published guidance on the administration and collection of convalescent plasma from patients who have recovered from COVID-19.[641] [642] There is currently insufficient evidence to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.[3] The Infectious Diseases Society of America recommends convalescent plasma only in the context of a clinical trial.[537] The authors of a Cochrane rapid review were uncertain as to whether convalescent plasma is beneficial for hospitalised patients with COVID-19. The completed studies were of poor quality, and the results could be related to natural progression of the disease or to other treatments the patient receives. There is limited information regarding adverse effects and very low-certainty evidence for safety in patients with COVID-19.[643]

## Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is being trialled in some patients with COVID-19.[32] [644] A retrospective study of 58 patients with severe COVID-19 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.[645] There is currently insufficient evidence to recommend IVIG for the treatment of COVID-19.[646] The National Institutes of Health guidelines panel recommends against the use of non-SARS-CoV-2-specific IVIG for the treatment of COVID-19 except in the context of a clinical trial.[3]

## Monoclonal antibody treatments

SARS-CoV-2 monoclonal antibodies have the potential to be used for prophylaxis and treatment of COVID-19.[647] Recombinant, fully human monoclonal neutralising antibodies, such as JS016 and LY-COV555, are in development. These antibodies bind to the SARS-CoV-2 surface spike protein receptor binding domain, which blocks the binding of the virus to the angiotensin-converting enzyme-2 (ACE2) host cell surface receptor. Both antibody treatments have started phase 1 studies.[648] [649] Novel multi-antibody cocktail therapies (e.g., REGN-COV2) are also in clinical trials for prophylaxis or treatment.[650]

## Interleukin-6 (IL-6) receptor antagonists

IL-6 receptor antagonist monoclonal antibodies (e.g., tocilizumab, sarilumab, siltuximab) are being trialled in COVID-19 patients for the treatment of virus-induced cytokine release syndrome. These drugs are already approved in some countries for other indications. A retrospective cohort study found that clinical improvement and 28-day mortality were not statistically different between tocilizumab and standard of care.[651] However, other studies have found that the use of tocilizumab was associated with significantly shorter duration of vasopressor support, reduced risk of non-invasive mechanical ventilation, and a reduction in mortality in patients with severe or critical disease.[652] [653] [654] [655] A meta-analysis of 7 retrospective studies found that there is no suggestion that tocilizumab provides any additional benefit for patients with severe disease; however, this was based on low-quality evidence and the study had many limitations.[656] Trials of sarilumab have been halted in the US as the drug failed to reach primary and key secondary end points.

## Anakinra



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Anakinra, an interleukin-1 inhibitor, is being trialled in COVID-19 patients for the treatment of virus-induced cytokine release syndrome. It is already approved in some countries for other indications. Addition of high-dose intravenous anakinra to non-invasive ventilation and standard care (which included hydroxychloroquine and lopinavir/ritonavir) in COVID-19 patients with moderate to severe acute respiratory distress syndrome and hyperinflammation was associated with a higher survival rate at 21 days in a small retrospective study.[657] A small prospective cohort study found that anakinra significantly reduced the need for invasive mechanical ventilation and mortality in patients with severe disease.[658] 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.[659] The National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of anakinra for the treatment of COVID-19.[3] The National Institute for Health and Care Excellence in the UK states that there is no evidence available to determine whether anakinra is effective, safe, or cost-effective for treating adults and children with secondary haemophagocytic lymphohistiocytosis triggered by SARS-CoV-2 or a similar coronavirus.[660]

## Mavrilimumab

Mavrilimumab, an anti-granulocyte–macrophage colony-stimulating factor receptor-alpha monoclonal antibody, was associated with improved clinical outcomes compared with standard care in non-mechanically ventilated patients with severe disease and systemic hyperinflammation in a single-centre prospective cohort study.[661]

## Janus kinase inhibitors

Janus kinase inhibitors (e.g., fedratinib, ruxolitinib, baricitinib) are currently in clinical trials for the treatment of COVID-19-associated cytokine release syndrome.[662] [663] [664] The National Institutes of Health guidelines panel recommends against the use of Janus kinase inhibitors for the treatment of COVID-19 except in the context of a clinical trial.[3]

## Stem cell therapy

Stem cell therapy is being investigated to treat patients with COVID-19 in clinical trials. It is thought that mesenchymal stem cells can reduce the pathological changes that occur in the lungs, and inhibit the cell-mediated immune inflammatory response.[665] The National Institutes of Health guidelines panel recommends against the use of mesenchymal stem cells for the treatment of COVID-19 except in the context of a clinical trial.[3] Adipose-derived mesenchymal stem cells have been approved by the FDA for the treatment of severe COVID-19.

## Bacille Calmette-Guerin (BCG) vaccine

The BCG vaccine is being trialled in some countries for the prevention of COVID-19, including in healthcare workers. There is some evidence that BCG vaccination prevents other respiratory tract infections in children and older people mediated by induction of innate immune memory.[666] However, there is no evidence to support its use in COVID-19, and the WHO does not recommend it for the prevention of COVID-19.[667]

## Bemcentinib

An experimental small molecule that inhibits AXL kinase. Bemcentinib has previously demonstrated a role in the treatment of cancer, but has also been reported to have antiviral activity in preclinical models, including activity against SARS-CoV-2. It was the first candidate to be selected as part of the UK's Accelerating COVID-19 Research and Development (ACCORD) study.[668] The study has stopped recruiting new patients into the trial due to the reduction of new COVID-19 cases in the UK. Patients already recruited will continue on treatment as per the study protocol.

## Angiotensin-II receptor antagonists

Angiotensin-II receptor antagonists such as losartan are being investigated as a potential treatment because it is thought that the angiotensin-converting enzyme-2 (ACE2) receptor is the main binding site for the




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virus.[669] [670] [671] However, some experts believe that these drugs may worsen COVID-19 due to overexpression of ACE2 in people taking these drugs.

## Other antivirals or antibiotics

Various other antiviral drugs (monotherapy and combination therapy) are being trialled in patients with COVID-19 (e.g., oseltamivir, darunavir, ganciclovir, favipiravir, baloxavir marboxil, umifenovir, ribavirin, interferon, leronlimab).[672] [673] [674] [675] [676] [677] [678] [679] [680] [681] There is no evidence to support the use of umifenovir.[682] Triple therapy with interferon beta-1b, lopinavir/ritonavir, and ribavirin has been tested in hospitalised COVID-19 patients in a small open-label randomised phase 2 trial. Patients who received triple therapy had a significantly shorter median time to a negative nasopharyngeal swab result compared with the control group (lopinavir/ritonavir only). Patients had mild to moderate disease at the time of enrollment.[683] The 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.[3] The PRINCIPLE trial in the UK is currently evaluating three treatment strategies in older people (people aged over 65 years, or people aged over 50 years with an underlying health condition): usual care alone; usual care plus azithromycin; and usual care plus doxycycline.[684]

## Ivermectin

Ivermectin, a broad-spectrum antiparasitic agent, has been shown to be effective against SARS-CoV-2 in vitro.[685] It is unclear whether the doses necessary to achieve antiviral activity against SARS-CoV-2 are attainable in humans.[686] Numerous registered clinical studies of ivermectin, either alone or in combination with other drugs (e.g., doxycycline, hydroxychloroquine), are ongoing in many countries for the treatment or prevention of COVID-19. Further research in randomised controlled trials is necessary.

## Vitamin C

Vitamin C supplementation has shown promise in the treatment of viral infections.[687] High-dose intravenous vitamin C is being trialled in some centres for the treatment of severe COVID-19.[688] There is no evidence to support or refute the use of vitamin C in the treatment of patients with COVID-19; however, a substantial number of trials are ongoing.[689] The National Institutes of Health guidelines panel states that there is insufficient data to recommend either for or against vitamin C.[3]

## Vitamin D

Vitamin D supplementation has been associated with a reduced risk of respiratory infections such as influenza in some studies.[690] [691] [692] Vitamin D is being trialled in patients with COVID-19.[693] [694] However, there is no evidence to recommend vitamin D for the prophylaxis or treatment of COVID-19 as yet.[695] The UK National Institute for Health and Care Excellence states that while there is no evidence to support taking vitamin D specifically to prevent or treat COVID-19, it does recommend that all people should take a vitamin D supplement daily as per UK government advice to maintain bone and muscle health during the pandemic, especially if they are not getting enough sun exposure due to shielding or self-isolating.[696] The National Institutes of Health guidelines panel states that there is insufficient data to recommend either for or against vitamin D.[3]

## Probiotics

There is emerging evidence that gut dysbiosis may have a role in the pathogenesis of COVID-19.[300] [301] [302] Probiotics may represent a complementary approach for the prevention or treatment of mucosal damage or inflammation through the modulation of gut microbiota; however, further research is required.[697]

## Traditional Chinese medicine

Traditional Chinese medicine is being used in patients with COVID-19 in China according to local guidelines and as part of clinical trials.[698]

## Hyperbaric oxygen



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Preliminary evidence suggests that hyperbaric oxygen treatment has been successfully used to treat deteriorating, severely hypoxaemic patients with severe COVID-19.[699] [700] Clinical trials are currently recruiting.[701] [702]

## Nitric oxide

Studies indicate that nitric oxide may help to reduce respiratory tract infection by inactivating viruses and inhibiting their replication in epithelial cells.[703] The FDA has approved an investigational drug application for inhaled nitric oxide to be studied in a phase 3 study of up to 500 patients with COVID-19. Other studies are currently recruiting.

## Aviptadil

A synthetic form of vasoactive intestinal peptide (also known as RLF-100) has been granted an expanded access protocol (which makes the treatment available to patients who have exhausted approved therapies and who are not eligible for the current clinical trial of aviptadil) for the treatment of respiratory failure in patients with COVID-19. Intravenous and inhaled formulations are currently in phase 2 and 3 clinical trials in the US.[704] [705]

## Icatibant

A selective bradykinin B2 receptor antagonist. A small exploratory case-control study of 9 people found an association between the administration of icatibant and improved oxygenation, suggesting that administration in the early stages of disease when patients are hypoxic may be beneficial. Treatment strategies that target the kallikrein-kinin system require further investigation in randomised trials for patients with COVID-19.[706]





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# Recommendations

## Monitoring

Regularly monitor the following in hospitalised patients to facilitate early recognition of deterioration and monitor for complications:[2] [857]

- Vital signs (temperature, respiratory rate, heart rate, blood pressure, oxygen saturation)
- Haematological 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

- Utilise medical early warning scores that facilitate early recognition and escalation of treatment of deteriorating patients (e.g., National Early Warning Score 2 [NEWS2], Paediatric Early Warning Signs [PEWS]) where possible.[2]
- There are no data on the value of using these scores in patients with COVID-19 in the primary care setting.[889]

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.[578] Perform fetal growth ultrasound 14 days after resolution of symptoms.[580]

## Patient instructions

General prevention measures

- Wash hands often with soap and water for at least 20 seconds or an alcohol-based hand sanitiser (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 1 metre [3 feet]) including shaking hands, particularly those who are sick, have a fever, or are coughing or sneezing. It is important to note that recommended distances differ between countries (for example, 2 metres [6 feet] 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).[307] [308]
- [BMJ Learning: Covid-19 – handwashing technique and PPE videos]
- [WHO: coronavirus disease (COVID-19) advice for the public]

Face masks

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- The World Health Organization (WHO) recommends that people with symptoms of COVID-19 should wear a medical mask, self-isolate, and seek medical advice as soon as possible. The WHO also now encourages the general public to wear medical or cloth masks in specific situations and settings (e.g., areas with known or suspected widespread transmission and limited or no capacity to implement other containment measures such as social distancing, contact tracing, and testing; settings where social distancing cannot be achieved, particularly in vulnerable populations).[96]
- The Centers for Disease Control and Prevention recommends that homemade cloth face coverings can be worn in public settings where social distancing measures are difficult to maintain (e.g., pharmacies, supermarkets), especially in areas where there is significant community transmission.[313]
- [WHO: coronavirus disease (COVID-19) advice for the public – when and how to use masks]
- [Public Health England: how to make a cloth face covering]
- [CDC: use of cloth face coverings to help slow the spread of COVID-19 (includes instructions on how to make masks)]

Travel advice

- Many countries have implemented international travel bans/closed their borders, have issued advice for domestic travel, and are requesting that citizens travelling abroad should come home immediately if they are able to. Some countries are restricting entry to foreign nationals who have been to affected areas in the preceding 14 days, or are enforcing 14-day quarantine periods where the person's health should be closely monitored (e.g., twice-daily temperature readings).
- Consult local guidance for specific travel restriction recommendations in your country:
  - [WHO: coronavirus disease (COVID-19) travel advice]
  - [CDC: coronavirus disease 2019 (COVID-19) – travel]
  - [NaTHNac: travel health pro]
  - [Public Health England: travel advice – coronavirus (COVID-19)]
  - [Smartraveller Australia: COVID-19]
  - [Government of Canada: coronavirus disease (COVID-19) – travel restrictions, exemptions, and advice]
  - [Ministry of Manpower Singapore: advisories on COVID-19]

Pets

- 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.[890]
- 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 emerging 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. A tiger tested positive in a zoo and two domestic pet cats tested positive in New York (both cats were owned by people with suspected or confirmed infection and both fully recovered).[891] [892] [893] [894] Transmission between cats has also been reported.[895]
- 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.[896]
- [CDC: coronavirus disease 2019 (COVID-19) – pets and other animals]

Athletes and highly active people

- Advise asymptomatic patients who test positive not to exercise for 2 weeks after their test result, with slow resumption of activity under the guidance of a healthcare team. Advise mildly


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symptomatic patients who test positive not to exercise until 2 weeks after symptom resolution and only after a thorough cardiac evaluation. If the assessment is normal, slow resumption of activity under the guidance of a healthcare team can be considered with close monitoring for clinical deterioration.[897]

Resources

- [WHO: coronavirus disease (COVID-19) pandemic]
- [CDC: coronavirus (COVID-19)]
- [NHS UK: coronavirus (COVID-19)]
- [NHS UK: COVID-19 patient rehabilitation booklet]
- [NHS UK: your COVID recovery]

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# Complications

| Complications | Timeframe | Likelihood |
|---|---|---|
| **comorbidities** | **short term** | **high** |

Data on the management of comorbidities in patients with COVID-19 is evolving rapidly. Tailor the management of COVID-19 to the patient's comorbidities (e.g., decide which chronic therapies should be continued and which therapies should be temporarily stopped, monitor for drug-drug interactions). For more information, see the Best Practice topic: Management of coexisting conditions in the context of COVID-19.

| | | |
|---|---|---|
| **venous thromboembolism** | **short term** | **high** |

Several studies have found a high incidence of thrombolytic complications in patients with COVID-19, even when thromboprophylaxis had been given.[769] The pooled prevalence of venous thromboembolism, pulmonary embolism, and deep vein thrombosis among all hospitalised patients was 21%, 15%, and 27%, respectively. These rates were higher in patients admitted to the intensive care unit.[770] The pooled prevalence of venous thromboembolism among intensive care patients receiving prophylactic or therapeutic anticoagulation was 31%.[771]

Coagulopathy in COVID-19 has a prothrombotic character, which may explain reports of thromboembolic complications.[772] 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).[535] Thrombotic events may be due to cytokine storm, hypoxic injury, endothelial dysfunction, hypercoagulability, and/or increased platelet activity.[773]

The risk factors with the most evidence for being predictive of venous thromboembolism are older age and elevated D-dimer levels.[769] Patients with very high D-dimer levels have the greatest risk of thrombosis and may benefit from active monitoring.[472] [473]

If venous thromboembolism is suspected, perform a computed tomographic angiography or ultrasound of the venous system of the lower extremities.[774]

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.[3]

Initial parenteral anticoagulation with a low molecular weight heparin or unfractionated heparin is preferred in acutely ill hospitalised 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.[533]

A high incidence (14.7%) of asymptomatic deep vein thrombosis was reported in a cohort of patients with COVID-19 pneumonia.[775] An autopsy study of 12 patients revealed deep vein thrombosis in 58% of patients in whom venous thromboembolism was not suspected before death.[776] 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.



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| Complications | Timeframe | Likelihood |
|---|---|---|

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.[777]

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.[778] [779] [780] [781] [782]

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 hypothesised 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.[783] [784] [785] However, this has not become accepted practice.

Cases of arterial thrombosis, cerebral venous thrombosis, and acute limb ischaemia secondary to thrombosis have been reported.[786] [787] [788] [789] [790]

| **cardiovascular complications** | **short term** | **medium** |
|---|---|---|

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.[791] [792] [793] These complications can occur on presentation or develop as the severity of illness worsens.[794]
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.[795]

Cardiovascular complications have been reported in 14.1% of patients during hospitalisation, with an overall case fatality rate of 9.6%. Patients with pre-existing 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%).[796] Cases of fulminant myocarditis, cardiac tamponade, cor pulmonale, takotsubo syndrome, and pericarditis have also been reported.[797] [798] [799] [800] [801]

Elevated cardiac biomarkers and emerging arrhythmia are associated with the development of severe COVID-19 and the need for intensive care admission.[802]

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 non-invasive or invasive ventilation, and have a higher risk of thromboembolic events and septic shock compared with patients without a history of cardiac disease.[794] [803] [804] [805] [806]

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. Results should be considered in the clinical context.[807]

Monitor blood pressure, heart rate, and fluid balance, and perform continuous ECG monitoring in all patients with suspected or confirmed acute myocardial injury.[807]

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.[795] It is important to consider that drugs such as hydroxychloroquine and azithromycin may

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| Complications | Timeframe | Likelihood |
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prolong the QT interval and lead to arrhythmias.[807] Guidelines for the management of COVID-19-related myocarditis are available.[808]

Infection may have longer-term implications for overall cardiovascular health; however, further research is required.[809] 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 pre-existing conditions, severity and overall course of the acute illness, and time from the original diagnosis.[810]

| **acute kidney injury** | **short term** | **medium** |
|---|---|---|

The overall incidence of acute kidney injury in patients with COVID-19 is approximately 10% to 17%; incidence is higher in patients with chronic kidney disease and those with severe or critical illness. The degree of acute kidney injury is closely associated with disease severity and prognosis. Approximately 5% to 7% of patients require renal replacement therapy. Patients have a poor prognosis, especially those who require renal replacement therapy.[811] [812] [813] [814] In a small UK cohort, 29% of hospitalised 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 paediatric inflammatory multisystem syndrome.[815]

Can develop at any time before or during hospital admission. Risk factors include age ≥65 years, Black ethnicity, history of acute kidney injury, chronic kidney disease, cardiovascular disease, hypertension, heart failure, hepatic disease, and diabetes.[816] [817] Causes include haemodynamic changes, hypovolaemia, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology, or rhabdomyolysis.[817] Direct kidney infection has been confirmed in an autopsy study of a single patient.[818]

Patients should meet criteria for acute kidney injury for diagnosis. [NHS England: acute kidney injury (AKI) algorithm] Perform a urinalysis for blood, protein, and glucose to help identify the underlying cause. Imaging is recommended if urinary tract obstruction is suspected.[817]

Stop any drugs that can cause or worsen acute kidney injury, if possible. Aim to achieve optimal fluid status (euvolaemia) in all patients. Consider a loop diuretic for treating fluid overload only. Manage hyperkalaemia according to local protocols. See local protocols for guidance on renal replacement therapy.[817]

Specialist input may be required in some cases (e.g., uncertainty about cause, abnormal urinalysis results, complex fluid management needs, indications for renal replacement therapy), and some patients may require critical care admission.[817] 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 haemodialysis if CRRT is not available or possible.[3]

Monitor fluid status daily, as well as serum urea, creatinine, and electrolytes at least every 48 hours (or more often if clinically indicated). Monitor patients for the development of, or progression to, chronic kidney disease for at least 2 to 3 years after acute kidney injury.[817]

Acute kidney injury is associated with poor prognosis.[816]

Cases of nephritis and collapsing glomerulopathy have been reported.[819] [820]

| **acute liver injury** | **short term** | **medium** |
|---|---|---|

The pooled prevalence of hepatic manifestations on admission is: elevated alanine aminotransferase (26.6%); elevated aspartate aminotransferase (37.2%); decreased albumin (45.6%); and elevated total bilirubin (18.2%). The incidence of acute hepatic injury was higher in Chinese populations and groups with a higher prevalence of pre-existing chronic liver disease; the incidence was similar in younger and older patients. Hepatic complications such as acute hepatic injury have been associated with an increased


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| Complications | Timeframe | Likelihood |
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risk of severe disease and mortality.[821] The prevalence of elevated aspartate aminotransferase was significantly higher in patients with severe disease (45.5%) compared with non-severe cases (15%).[822]

Risk factors associated with severe liver injury include older age, pre-existing liver disease, and severe COVID-19.[823]

Medications used in the treatment of COVID-19 (e.g., lopinavir/ritonavir) may have a detrimental effect on liver injury.[823]

Guidelines on the management of liver derangement in patients with COVID-19 have been published.[824]

| **neurological complications** | **short term** | **medium** |
|---|---|---|

Patients with severe illness commonly have central or peripheral neurological complications, possibly due to viral invasion of the central nervous system (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] has been detected in the brain and cerebrospinal fluid) or systemic illness.

Neurological symptoms have been reported in 36% to 57% of patients in case series, and were more common in patients with severe illness.[825] [826] In a small retrospective study of patients in an intensive care unit, 44% of patients with neurological symptoms had abnormal findings on brain magnetic resonance imaging.[827]

Complications include acute cerebrovascular disease, impairment of consciousness, ataxia, neuralgia, seizures, musculoskeletal injury, corticospinal tract signs, meningitis, encephalitis, encephalopathy, encephalomyelitis, transverse myelitis, intracerebral haemorrhage, cerebral venous sinus thrombosis, rhabdomyolysis and other muscle disease, myasthenia gravis, and Guillain-Barre syndrome and other neuropathies. Patients may present with these signs/symptoms, or they may develop them during the course of the disease.[828] [829] [830] [831]

Ischaemic stroke has been reported in 1.6% of adults with COVID-19 who visited the accident and emergency department or were hospitalised.[832] It 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.[833] Guidelines for the management of acute ischaemic stroke in patients with COVID-19 infection have been published.[834]

Patients may show cerebral changes on magnetic resonance imaging months after recovery, suggesting that long-term consequences may be possible.[835]

| **cytokine release syndrome** | **short term** | **low** |
|---|---|---|

Cytokine release syndrome may cause ARDS or multiple-organ dysfunction, which may lead to death.[836] Elevated serum proinflammatory cytokines (e.g., tumour 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 haemophagocytic lymphohistiocytosis, which may be fatal.[31] [431] [482] [837] Interleukin-6, in particular, has been associated with severe COVID-19 and increased mortality.[838]

One study found that patients who require admission to the intensive care unit have significantly higher levels of interleukin-6, interleukin-10, and tumour necrosis factor alpha, and fewer CD4+ and CD8+ T cells.[839]

Anti-inflammatory/immunosuppressive treatments (e.g., tocilizumab, hydroxychloroquine/chloroquine, Janus kinase inhibitors) are being trialled in COVID-19 patients.[840] See Emerging section for more information.

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| Complications | Timeframe | Likelihood |
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Cytokine release syndrome has been reported in children, although cases appear to be rare.[841] See section below on paediatric inflammatory multisystem syndrome.

| **paediatric inflammatory multisystem syndrome** | **short term** | **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 post-infectious inflammatory process. The syndrome has a strong temporal association with SARS-CoV-2 infection.[842] [843] [844] Also known as PIMS, multisystem inflammatory syndrome in children (MIS-C), paediatric 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.[351] [844] [845] [846] Most patients have fever, as well as features of shock, cardiac involvement (e.g., elevated cardiac markers, congestive heart failure, cardiac dysfunction, myocarditis, coronary artery dilatation or aneurysm, hypotension, pericardial effusion, mitral regurgitation), gastrointestinal symptoms (e.g., abdominal pain, vomiting, diarrhoea), and significantly elevated inflammatory markers.[842] [843]

A systematic review of 8 studies from the US and Europe found that the median age of patients ranged from 7 to 10 years of age, and 59% of patients were male. In regards to ethnicity, 31% to 62% were Black and 36% to 39% were Hispanic. The proportion of patients with a positive SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) test result ranged from 13% to 69%, and the proportion with a positive serology test ranged from 75% to 100%. Gastrointestinal symptoms were prominent (87%), as were dermatological/mucocutaneous (73%) and cardiovascular symptoms (71%). Respiratory, neurological, and musculoskeletal symptoms were less frequent. Serum ferritin and D-dimer levels were elevated in at least 50% of patients, and C-reactive protein, interleukin-6, and fibrinogen levels were elevated in at least 75% of patients. Cardiac markers were elevated in the majority of patients. Thrombocytopenia was common. The mortality rate was 2%.[842]

In a multicentre observational study in the UK, 78 cases were reported across 21 paediatric intensive care units. 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 diarrhoea 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.[847]

Management is mainly supportive and involves a multidisciplinary team (paediatric infectious disease, cardiology, rheumatology, critical care). Patients are commonly managed with intravenous immunoglobulin, vasopressor support, corticosteroids, immune modulators, anticoagulation, antiplatelet therapy, and respiratory support.[842] [843]

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.[848] 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.[849]

Cases of COVID-19-associated Kawasaki-like multisystem inflammatory disease have been reported in adults.[850] [851] [852]

| **septic shock** | **short term** | **low** |
|---|---|---|

Reported in 4% to 8% of patients in case series.[31] [32] [423] [853]

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. Noradrenaline (norepinephrine)



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| Complications | Timeframe | Likelihood |
|---|---|---|

is the preferred first-line agent, with vasopressin or adrenaline (epinephrine) considered suitable alternatives. Vasopressin can be added to noradrenaline if target mean arterial pressure cannot be achieved with noradrenaline alone.[3] [510] Dopamine is only recommended as an alternative vasopressor in certain patients (e.g., those with a low risk of bradycardia or tachyarrhythmias). Dobutamine is recommended in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressors. Low-dose corticosteroid therapy is recommended for refractory shock.[3]

| **disseminated intravascular coagulation** | **short term** | **low** |
|---|---|---|

Reported in 71% of non-survivors.[854] 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/haemorrhage or venous thromboembolism.[855]

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.[856]

Prophylactic-dose low molecular weight heparin should be considered in all hospitalised patients with COVID-19 (including those who are not critically ill), unless there are contraindications. This will also protect against venous thromboembolism.[857] 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.[858] In patients with heparin-induced thrombocytopenia (or a history of it), argatroban or bivalirudin are recommended.[855]

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.[856] [857]

| **acute respiratory failure** | **short term** | **low** |
|---|---|---|

Reported in 8% of patients in case series.[32]

Leading cause of mortality in patients with COVID-19.[734]

Children can quickly progress to respiratory failure.[8]

| **pregnancy-related complications** | **short term** | **low** |
|---|---|---|

Retrospective reviews of pregnant women with COVID-19 found that women appeared to have fewer adverse maternal and neonatal complications and outcomes than would be expected for those with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). Adverse effects on the newborn including fetal distress, respiratory distress, thrombocytopenia, and abnormal liver function have been reported; however, it is unclear whether these effects are related to maternal SARS-CoV-2 infection. Maternal deaths have been reported, as well as miscarriage (including a case in the second trimester), ectopic pregnancy, intrauterine growth restriction, oligohydramnios, perinatal death, preterm birth, and neonatal death. It is unclear whether these effects are related to COVID-19.[593] [859] [860] [861] [862] [863] [864] [865] [866] [867] [868] While the rate of stillbirth increased during the pandemic in one centre in London, it is unknown whether this is related to SARS-CoV-2 infection.[869]

Approximately 3% of pregnant women require intensive care admission. The preterm birth rate is 20%, and the neonatal death rate is 0.3%.[870] In the UK, 25% of births were preterm, 10% of women required respiratory support, 1% of women died, and 5% of babies tested positive for SARS-CoV-2. Almost 60% of women gave birth by caesarean section, although most caesarean births were for indications other than maternal compromise due to COVID-19.[17] In Spain, severe adverse maternal outcomes occurred in 11% of pregnant women, and caesarean delivery was independently associated with an increased risk

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| Complications | Timeframe | Likelihood |
|---|---|---|
| of maternal clinical deterioration and neonatal intensive care unit admission.[871] In the US, caesarean delivery rates were higher in patients with COVID-19 compared with patients without in one cohort. Postnatal complications (fever, hypoxia, readmission) occurred in 13% of infected women compared with 4.5% of women without COVID-19.[872] | | |
| **aspergillosis** | **short term** | **low** |
| Invasive pulmonary aspergillosis has been reported in critically ill patients with moderate to severe ARDS.[873] [874] [875] A prospective observational study found that one third of mechanically ventilated patients with COVID-19 had putative invasive pulmonary aspergillosis.[876]<br><br>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 radiological or clinical features.[550] [877]<br><br>Prescribe appropriate antifungal therapy according to local guidelines.[878] | | |
| **pancreatic injury** | **short term** | **low** |
| Mild pancreatic injury (defined as elevated serum amylase or lipase levels) has been reported in 17% of patients in one case series.[879] 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.[880] [881] Prior history of pancreatitis does not appear to be a risk factor for pancreatic inflammation in patients with COVID-19.[882] | | |
| **autoimmune haemolytic anaemia** | **short term** | **low** |
| Warm or cold autoimmune haemolytic anaemia (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 haemolytic anaemia is related to COVID-19 infection.[883] | | |
| **immune thrombocytopenia** | **short term** | **low** |
| A small number of cases of immune thrombocytopenia have been reported in patients with COVID-19, including one case report in a 10-year-old child and another in a pregnant woman.[884] [885] [886] | | |
| **subacute thyroiditis** | **short term** | **low** |
| Cases of subacute thyroiditis have been reported in patients with COVID-19 who require intensive care.[887] 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.[888] | | |

# Prognosis

## Case fatality rate

The overall global case fatality rate (CFR), defined as the total number of deaths reported divided by the total number of infections reported, is currently estimated to be 3.5% based on World Health Organization data as of 17 August 2020. The CFR varies considerably between countries.[707]



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The overall CFR in China has been estimated to be 2.3% (0.9% in patients without comorbidities) based on a large case series of 72,314 reported cases from 31 December 2019 to 11 February 2020 (mainly among hospitalised patients).[4] However, another study estimates the CFR in China to be lower at 1.38% (after adjusting the crude estimate for censoring, demography, and under-ascertainment).[708]

The overall cumulative incidence of death 90 days after the start of a study in over 10,000 COVID-19 patients in England was <0.01% in those aged 18 to 39 years, and 0.67% and 0.44% in men and women, respectively, in patients aged 80 years and older. Increased risk of death was associated with factors including increasing age, being male, Black and South Asian ethnicity, and comorbidities such as diabetes, severe asthma, and various other medical conditions.[709]

These figures need to be interpreted with extreme caution. In pandemics, CFRs tend to start high and then trend downwards as more data becomes available. For example, at the start of the 2009 H1N1 influenza pandemic the CFR varied from 0.1% to 5.1% (depending on the country), but the mortality rate ended up being around 0.02%.[710] [Centre for Evidence-Based Medicine: global COVID-19 case fatality rates]

Factors that affect the CFR include:

- Increased case detection of patients with severe disease
- Testing limitations (some countries are only testing patients who have severe symptoms)
- Testing rates in each country
- Delays between symptom onset and death
- Local factors (e.g., patient demographics, availability and quality of health care, other endemic diseases).

It is important to note that daily death counts need to be interpreted with caution. 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.[711]

In Italy, the CFR may be higher because Italy has the second oldest population in the world, the highest rates of antibiotic resistance deaths in Europe, and a higher incidence of smoking (a known risk factor for more severe disease). The way COVID-19 related deaths are identified and reported in Italy may have also resulted in an overestimation of cases. Patients who die 'with' COVID-19 and patients who die 'from' COVID-19 are both counted towards the death toll. Only 12% of death certificates have shown direct causality from COVID-19, while 88% of patients who have died had at least one comorbidity.[710] [712]

The overall CFR appears to be less than that reported for severe acute respiratory syndrome coronavirus (SARS) (10%) and Middle East respiratory syndrome (MERS) (37%).[31] Despite the lower CFR, COVID-19 has so far resulted in more deaths than both SARS and MERS combined.[713]

## Infection fatality rate

The infection fatality rate (IFR) is the proportion of deaths among all infected individuals including confirmed cases, undiagnosed cases (e.g., mildly symptomatic or asymptomatic cases), and unreported cases. While the CFR is subject to selection bias as more severe/hospitalised cases are tested, the IFR gives a more accurate picture of the lethality of a disease, especially as testing becomes more rigorous within a population. The Centers for Disease Control and Prevention's current best estimate of the overall IFR is 0.65%.[714]

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 could be much lower.[715]

Evidence from seroprevalence studies suggests that the prevalence of infections is much higher than the official figures suggest, and that the virus is much less lethal than the current global case and death counts indicate.

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- UK: data from the first round of results of the UK Biobank COVID-19 antibody study indicate that 7.1% of participants had been infected previously overall. Previous infection was most common among people who lived in London (10.4%), and least common among those who lived in the south west of England and Scotland (4.4% in both).[716] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies were measured in the community at an overall adjusted prevalence of 6% in England (20 June to 13 July 2020).[717]
- US: seroprevalence estimates for 10 sites in the US (Connecticut, Louisiana, Minnesota, Missouri, New York City metro area, Philadelphia, San Francisco Bay Area, South Florida, Utah, and Western Washington State) are available from the Centers for Disease Control and Prevention. In the New York City metro area, the number of estimated infections is at least 7 times higher than the number of cases reported according to the latest figures reported for the period 15 to 21 June.[718] [CDC: interactive serology dashboard for commercial laboratory surveys]
- Spain: seroprevalence estimates from a nationwide study indicate a seroprevalence of around 5%, with the prevalence in hotspots (e.g., Madrid) being five times higher than that in low-risk regions.[719]
- Switzerland: seroprevalence data from Geneva indicate an IFR of 0.64% for the total population, and an IFR of 0.0092% for people aged 20 to 49 years, 0.14% for people aged 50 to 64 years, and 5.6% for people aged 65 years and older.[720]
- Iran: the seroprevalence estimate after adjusting for population and test performance characteristics in Guilan province was 22% to 33%, resulting in an estimated IFR of 0.08% to 0.12%.[721]
- Denmark: a seroprevalence study in blood donors estimates the IFR to be approximately 0.08% in people aged under 70 years.[722]
- Los Angeles county, California: based on results of the first round of testing, a research team estimates that approximately 2.8% to 5.6% of the county's adult population has antibodies to the virus, an estimated IFR of 0.1% to 0.2% based on current deaths in the county.[723] Published seroprevalence data from adults in Los Angeles county found that the community prevalence of SARS-CoV-2 antibodies was 4.65% in early April. Based on this figure, the authors estimate that approximately 367,000 county residents had SARS-CoV-2 antibodies. This is much higher than the number of confirmed infections at this time, which was 8430. They conclude that fatality rates based on the number of confirmed cases may be much higher than the rates based on the actual number of infections.[724]
- Santa Clara county, California: an analysis of 3300 people in early April found that the seroprevalence of antibodies to SARS-CoV-2 in Santa Clara county was between 2.49% and 4.16%. Based on this, researchers estimate that between 48,000 and 81,000 people were infected with the virus at the time (out of the county's population of approximately 2 million people). Researchers estimate an IFR of 0.1% to 0.2% based on this data.[725]
- Germany: the overall seroprevalence in healthcare workers in a tertiary hospital was low (1.6%).[726]
- Iceland: the country where the most testing per capita has occurred - the IFR lies between 0.01% and 0.19%.[710]
- China: seropositivity varied between 3.2% and 3.8% in Wuhan, and decreased in other Chinese cities as the distance to the epicentre increased.[727]

These estimates are likely to change as more data emerge.

## Case fatality rate according to age and presence of comorbidities

The CFR increases with age.[708] The presence of comorbidities is associated with greater disease severity and poor clinical outcomes, and the risk increases with the number of comorbidities a patient has.[728]

The majority of deaths in China have been in patients aged 60 years and older and/or those who have pre-existing underlying health conditions (e.g., hypertension, diabetes, cardiovascular disease). The CFR was highest among critical cases (49%). It was also higher in patients aged 80 years and older (15%), males (2.8% versus 1.7% for females), and patients with comorbidities (10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6% for hypertension, and 5.6% for cancer).[4] Another study found the CFR in China to be 6.4% in patients aged ≥60 years versus 0.32% in patients aged <60 years, and 13.4% in patients aged ≥80 years.[708]

In Italy, the CFR was 8.5% in patients aged 60 to 69 years, 35.5% in patients aged 70 to 79 years, and 52.5% in patients aged ≥80 years.[729] In a case series of 1591 critically ill patients in Lombardy, the majority of patients were older men, a large proportion required mechanical ventilation and high levels of positive end-expiratory pressure, and the mortality rate in the intensive care unit was 26%.[730]


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In the US, the CFR was highest among patients aged ≥85 years (10% to 27%), followed by those aged 65 to 84 years (3% to 11%), 55 to 64 years (1% to 3%), 20 to 54 years (<1%), and ≤19 years (no deaths). Patients aged ≥65 years accounted for 80% of deaths.[7] The CFR among critically ill patients admitted to the intensive care unit reached 67% in one hospital in Washington state. Most of these patients had underlying health conditions, with congestive heart failure and chronic kidney disease being the most common.[731] The CFR in residents in a long-term care facility in Washington was reported to be 34%.[732]

The case fatality rate in patients with cancer was 37% for patients with haematological malignancies and 25% for solid malignancies in one study. Some 55% of lung cancer patients died from COVID-19.[733]

Children have a good prognosis and generally recover within 1 to 2 weeks, and deaths are rare.[16]

## Prognostic factors

The leading cause of death in patients with COVID-19 is respiratory failure from acute respiratory distress syndrome.[734] The overall pooled mortality rate from acute respiratory distress syndrome in COVID-19 patients is 39%; however, this varies significantly between countries (e.g., China 69%, Iran 28%, France 19%, Germany 13%).[571] Patients who required invasive mechanical ventilation had an 88% mortality rate in one study in New York, but it has been much lower (36% to 53%) in other studies.[735] [736] [737] The other most common complications in deceased patients are myocardial injury, liver or kidney injury, and multi-organ dysfunction.[738] The strongest predictor of in-hospital mortality was chronic pulmonary disease, followed by chronic cardiovascular disease, older age, and elevated interleukin-6 and D-dimer levels at admission in a New York study.[549] In one retrospective study of 52 critically ill patients in Wuhan City, 61.5% of patients died by 28 days, and the median time from admission to the intensive care unit to death was 7 days for patients who didn't survive.[739]

Prognostic factors that have been associated with increased risk of unfavourable outcomes and mortality include:[740]

- Age ≥50 years
- Male sex
- Smoking
- Presence of comorbidities (e.g., hypertension, diabetes, cardiovascular or cerebrovascular disease, COPD, obesity, malignancy)
- Lymphopenia
- Thrombocytopenia
- Liver, kidney impairment, or cardiac injury
- Elevated inflammatory markers (C-reactive protein, procalcitonin, ferritin)
- Elevated D-dimer
- Elevated interleukin-6.

The most common risk factors for death are age ≥65 years, male sex, hypertension, cardiovascular disease, diabetes, chronic obstrictive pulmonary disease, and cancer.[741]

## Prognostic scores

The APACHE II score was found to be an effective clinical tool to predict hospital mortality in patients with COVID-19, and performed better than SOFA and CURB-65 scores in a small retrospective observational study. An APACHE II score of 17 or more was an early indicator of death and may help provide guidance to make further clinical decisions.[742] In another retrospective study, A-DROP (a modified version of CURB-65) showed better accuracy of in-hospital death prediction on admission compared with other widely used community-acquired pneumonia scores.[743] Further research is required to confirm these findings, and to validate the use of prognostic scores in patients with COVID-19.

New clinical risk scores to predict disease progression and the risk for critical illness in hospitalised patients with COVID-19 have been developed (e.g., COVID-GRAM, CALL score).[744] [745] COVID-GRAM, a web-based calculator to estimate the probability that a patient will develop critical illness (defined as intensive care admission, invasive ventilation, or death) has been validated in a study of nearly 1600 patients in

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China. It relies on the following 10 variables at admission: chest radiographic abnormality, age, haemoptysis, dyspnoea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin. Additional validation studies, especially outside of China, are required.[745]

## Refractory disease

Refractory disease (patients who do not reach obvious clinical and radiological remission within 10 days after hospitalisation) has been reported in nearly 50% of hospitalised patients in one retrospective single-centre study of 155 patients in China. Risk factors for refractory disease include older age, male sex, and the presence of comorbidities. These patients generally require longer hospital stays as their recovery is slower.[746]

## Infectivity of recovered cases

Potential infectivity of recovered cases is still unclear. There have been case reports of patients testing positive again after being discharged (i.e., after symptom resolution and two consecutive negative test results two days apart). This suggests that some patients in convalescence may still be contagious, although this is yet to be confirmed.[747] [748]

## Reinfection/reactivation

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection/reactivation has been reported in patients after hospital discharge. These patients return a positive reverse-transcription polymerase chain reaction (RT-PCR) test again after two negative RT-PCR tests and after hospital discharge.[749] [750] [751] [752] [753] [754] It is unclear whether these cases are reinfections/relapses/reactivations, or whether the test result was a false-negative at the time of discharge. It has been suggested that retesting positive may be due to discontinuing antiviral treatment in one patient.[755] In a small cross-sectional study, 10 out of 60 patients had a positive RT-PCR from 4 to 24 days after index hospital discharge, presumed to be due to persistent viral shedding rather than reinfection.[756] Increasing the number of consecutive RT-PCR negative test results from 2 to 3 decreases the rate of recurrent RT-positive tests after discharge by approximately 4-fold.[757] Further research is required.

## Post-infection immunity

Most convalescent patients have detectable neutralising antibodies and cellular immune responses.[758] A study in macaques suggests that infection with SARS-CoV-2 offers protection against reinfection.[759] There are no good data available yet on whether patients have immunity from reinfection after recovery. However, the limited data available suggest that recovery from COVID-19 might confer immunity against reinfection.[760] There are data to suggest that asymptomatic people may have a weaker immune response to infection; however, this is yet to be confirmed.[761] Among 175 patients who recovered from mild disease in China, neutralising antibody titres to SARS-CoV-2 varied substantially.[762]

## Post-acute COVID-19 and recovery

While most patients recover within 2 weeks, approximately 10% of patients still have symptoms after 3 weeks, and some may have symptoms for months, according to data from the UK COVID Symptom Study in which people enter their ongoing symptoms on a smartphone app.[763] The term ‘long COVID’ has been used to describe post-acute COVID-19 symptoms.[764]

Nearly 90% of hospitalised 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.[765] 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 aged 18 to 34 years with no underlying chronic medical conditions, 20% had not returned to their usual state of health.[766]

Symptoms vary widely, may relapse and remit, and can occur in those with mild disease only. Common long-term symptoms include cough, low-grade fever, and fatigue. Dyspnoea, chest pain, myalgia, headaches, rashes, gastrointestinal symptoms, neurocognitive difficulties, and mental health conditions have also been


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reported. Blood tests should be ordered selectively and for specific clinical indications after a careful history and examination. Other investigations may include chest x-ray, urine tests, and an electrocardiogram.[767]

There are no definitive, evidence-based recommendations for the management of post-acute COVID-19 as yet; therefore, patients should be managed pragmatically and symptomatically (e.g., antipyretic for fever, breathing techniques for chronic cough, home pulse oximetry for monitoring breathlessness, pulmonary rehabilitation, staged return to exercise). 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 neurological symptoms that are new, persistent, or progressive.[767]

Patients who are discharged from hospital may have immediate and longer-term health needs including physical (e.g., pulmonary and cardiac rehabilitation, tracheostomy wounds, pressure ulcers, dysphagia, chronic cough, fatigue, neuropathy, muscular weakness, long-term risk of chronic respiratory disorders), psychological and neuropsychological (e.g., delirium, cognitive impairment, post-traumatic stress disorder, anxiety, depression), and social (e.g., impaired activities of daily living).[768]

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thebmj Visual summary

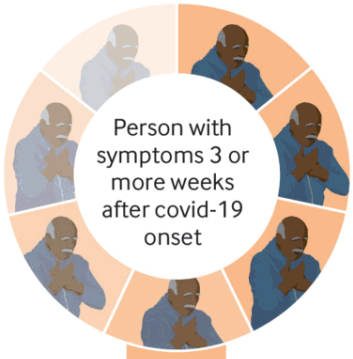
# "Long covid" in primary care

Assessment and initial management of patients with continuing symptoms

Post-acute covid-19 appears to be a multi-system disease, sometimes occurring after a relatively mild acute illness. Clinical management requires a whole-patient perspective. This graphic summarises the assessment and initial management of patients with delayed recovery from an episode of covid-19 that was managed in the community or in a standard hospital ward.

## An uncertain picture

The long term course of covid-19 is unknown. This graphic presesents an approach based on evidence available at the time of publication. However, caution is advised, as patients may present atypically, and new treatments are likely to emerge




## Investigations

Clinical testing is not always needed, but can help to pinpoint causes of contiuing symptoms, and to exclude conditions like pulmonary embolism or myocarditis. Examples are provided below:

**Blood tests**

- Full blood count
- Electrolytes
- Liver and renal function
- Troponin
- C reactive protein
- Creatine kinase
- D-dimer
- Brain natriuretic peptides
- Ferritin – to assess inflammatory and prothrombotic states

**Other investigations**

- Chest x ray
- Urine tests
- 12 lead electrocardiogram

## Clinical assessment

04

**Full history**
From date of first symptom

**Current symptoms**
Nature and severity

**Examination, for example:**

- Temperature
- Heart rate and rhythm
- Blood pressure
- Respiratory examination
- Functional status
- Pulse oximetry
- Clinical testing

If indicated

## Managing comorbidities

Many patients have comorbidities including diabetes, hypertension, kidney disease or ischaemic heart disease. These need to be managed in conjuntion with covid-19 treatment. Refer to condition specific guidance, available in the associated article by Greenhalgh and colleagues

Assess comorbidities

Social and financial circumstances

## Social, financial, and cultural support

Prolonged covid-19 may limit the ability to engage in work and family activities. Patients may have experienced family bereavements as well as job losses and consequent financial stress and food poverty. See the associated article by Greenhalgh and colleagues for a list of external resources to help with these problems

## Safety netting and referral

The patient should seek medical advice if concerned, for example:

- Worsening breathlessness
- $PaO_2$ < 96%
- Unexplained chest pain
- New confusion
- Focal weakness

Specialist referral may be indicated, based on clinical findings, for example:

- **Respiratory** if suspected pulmonary embolism, severe pneumonia
- **Cardiology** if suspected myocardial infarction, pericarditis, myocarditis or new heart failure
- **Neurology** if suspected neurovascular or acute neurological event

**Pulmonary rehabilitation** may be indicated if patient has persistent breathlessness following review

## Medical management

- Symptomatic, such as treating fever with paracetamol
- Optimise control of long term conditions
- Listening and empathy
- Consider antibiotics for secondary infection
- Treat specific complications as indicated

## Self management

- Daily pulse oximetry
- Attention to general health
- Rest and relaxation
- Self pacing and gradual increase in exercise **if tolerated**
- Set achievable targets

- Diet
- Sleep
- Quitting smoking
- Limiting alcohol
- Limiting caffeine

## Mental health

In the consultation:

- Continuity of care
- Avoid inappropriate medicalisation
- Longer appointments for patients with complex needs (face to face if needed)

In the community:

- Community linkworker
- Patient peer support groups
- Attached mental health support service
- Cross-sector partnerships with social care, community services, faith groups

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# Diagnostic guidelines

## Europe

### Assessment of COVID-19 in primary care

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### COVID-19 position statement: presentations and management of COVID-19 in older people in acute care

**Published by:** Scottish Intercollegiate Guidelines Network **Last published:** 2020

### COVID-19: guidance for health professionals

**Published by:** Public Health England **Last published:** 2020

### COVID-19 pandemic

**Published by:** European Centre for Disease Prevention and Control **Last published:** 2020

## International

### Country & technical guidance - coronavirus disease (COVID-19)

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

### Laboratory testing strategy recommendations for COVID-19

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

### Laboratory testing for coronavirus disease (COVID-19) in suspected human cases

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

### Public health surveillance for COVID-19: interim guidance

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

### Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed

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

### Use of chest imaging in COVID-19

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## North America

### Overview of testing for SARS-CoV-2

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Interim guidelines for COVID-19 antibody testing

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 (COVID-19) pandemic

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Infectious Diseases Society of America guidelines on the diagnosis of COVID-19

**Published by:** Infectious Diseases Society of America **Last published:** 2020

### Infectious Diseases Society of America guidelines on infection prevention in patients with suspected or known COVID-19

**Published by:** Infectious Diseases Society of America **Last published:** 2020

### COVID-19 resource center

**Published by:** Infectious Diseases Society of America **Last published:** 2020

### Clinical guidance

**Published by:** American Academy of Pediatrics **Last published:** 2020

## Asia

### A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia

**Published by:** Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team; Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care **Last published:** 2020

### Diagnosis and clinical management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

**Published by:** Peking Union Medical College Hospital **Last published:** 2020



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# Treatment guidelines

## Europe

### Coronavirus specialty guides

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### COVID-19 rapid guideline: critical care in adults

**Published by:** National Institute for Health and Care Excellence **Last published:** 2020

### Coronavirus (COVID-19): rapid guidelines and evidence reviews

**Published by:** National Institute for Health and Care Excellence **Last published:** 2020

### COVID-19: guidance for health professionals

**Published by:** Public Health England **Last published:** 2020

### BMJ's coronavirus (covid-19) hub

**Published by:** BMJ **Last published:** 2020

### COVID-19 pandemic

**Published by:** European Centre for Disease Prevention and Control **Last published:** 2020

### COVID-19: information for the respiratory community

**Published by:** British Thoracic Society **Last published:** 2020

### COVID-19 position statement: presentations and management of COVID-19 in older people in acute care

**Published by:** Scottish Intercollegiate Guidelines Network **Last published:** 2020

### Community palliative, end of life and bereavement care in the COVID-19 pandemic

**Published by:** Royal College of General Practitioners; Association for Palliative Medicine **Last published:** 2020

### After-care needs of inpatients recovering from COVID-19

**Published by:** NHS England **Last published:** 2020

### Coronavirus (COVID-19) infection in pregnancy

**Published by:** Royal College of Obstetricians and Gynaecologists **Last published:** 2020

### Recommendations for COVID-19 clinical management

**Published by:** National Institute for the Infectious Diseases (Italy) **Last published:** 2020

### Recommendations on the clinical management of the COVID-19 infection by the new coronavirus SARS-CoV2

**Published by:** Spanish Paediatric Association **Last published:** 2020





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## International

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### Clinical management of COVID-19: interim guidance

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### Home care for patients with suspected or confirmed COVID-19 and management of their contacts

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

### Criteria for releasing COVID-19 patients from isolation

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

### Advice on the use of masks in the context of COVID-19

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

### Rapid advice guidelines for management of children with COVID-19

**Published by:** International multidisciplinary working group **Last published:** 2020

### COVID-19 guidance and the latest research in the Americas

**Published by:** Pan American Health Organization **Last published:** 2020

### ISTH interim guidance on recognition and management of coagulopathy in COVID#19

**Published by:** International Society of Thrombosis and Haemostasis **Last published:** 2020

### Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19)

**Published by:** Surviving Sepsis Campaign **Last published:** 2020

### Labor and delivery guidance for COVID-19

**Published by:** International working group **Last published:** 2020

### Global interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium from FIGO and allied partners: information for healthcare professionals

**Published by:** International Federation of Gynecology and Obstetrics **Last published:** 2020

### ISUOG interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium: information for healthcare professionals – an update

**Published by:** International Society of Ultrasound in Obstetrics and Gynecology **Last published:** 2020



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## North America

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### Information for healthcare professionals about coronavirus (COVID-19)

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19)

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Information for clinicians on investigational therapeutics for patients with COVID-19

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19)

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Discontinuation of transmission-based precautions and disposition of patients with COVID-19 in healthcare settings (interim guidance)

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Discontinuation of isolation for persons with COVID-19 not in healthcare settings

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Interim U.S. guidance for risk assessment and work restrictions for healthcare personnel with potential exposure to COVID-19

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19

**Published by:** Infectious Diseases Society of America **Last published:** 2020

### COVID#19: interim guidance on management pending empirical evidence

**Published by:** American Thoracic Society **Last published:** 2020

### COVID-19 resource center

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### Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019

**Published by:** CHEST Guideline and Expert Panel **Last published:** 2020



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### Clinical guidance

**Published by:** American Academy of Pediatrics **Last published:** 2020

### Evaluation and management considerations for neonates at risk for COVID-19

**Published by:** Centers for Disease Control and Prevention **Last published:** 2020

### Management of infants born to mothers with suspected or confirmed COVID-19

**Published by:** American Academy of Pediatrics **Last published:** 2020

### Novel coronavirus 2019 (COVID-19)

**Published by:** American College of Obstetricians and Gynecologists **Last published:** 2020

### Coronavirus disease (COVID-19): outbreak update

**Published by:** Government of Canada **Last published:** 2020



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## Asia

### Management of critically ill patients with COVID-19 in ICU: statement from front-line intensive care experts in Wuhan, China

**Published by:** Chinese expert working panel **Last published:** 2020

### Coronavirus disease

**Published by:** Chinese Center for Disease Control and Prevention **Last published:** 2020

### Handbook of COVID-19 prevention and treatment

**Published by:** First Affiliated Hospital, Zhejiang University School of Medicine **Last published:** 2020

### A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia

**Published by:** Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team; Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care **Last published:** 2020

### Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7)

**Published by:** National Health Commission of the People's Republic of China; National Administration of Traditional Chinese Medicine of the People's Republic of China **Last published:** 2020

### Diagnosis and clinical management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

**Published by:** Peking Union Medical College Hospital **Last published:** 2020

### Updates on COVID-19 (coronavirus disease 2019) local situation

**Published by:** Ministry of Health Singapore **Last published:** 2020

### New coronavirus (COVID-19)#

**Published by:** National Institute of Infectious Diseases Japan **Last published:** 2020

### New coronavirus infection

**Published by:** Japanese Association for Infectious Diseases **Last published:** 2020

### Perinatal and neonatal management plan for prevention and control of SARS-CoV-2 infection (2nd edition)

**Published by:** Working Group for the Prevention and Control of Neonatal SARS-CoV-2 Infection in the Perinatal Period of the Editorial Committee of Chinese Journal of Contemporary Pediatrics **Last published:** 2020



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# Oceania

## Coronavirus disease 2019 (COVID-19)

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# Online resources

1. American Academy of Pediatrics: children and COVID-19 – state-level data report *(external link)*
2. Johns Hopkins University: coronavirus COVID-19 global cases *(external link)*
3. BMJ talk medicine podcast: Covid-19 update *(external link)*
4. BMJ Best Practice: Management of co-existing conditions in the context of COVID-19 *(external link)*
5. WHO: coronavirus disease (COVID-19) emergency dashboard *(external link)*
6. WHO: coronavirus disease (COVID-2019) weekly epidemiological updates *(external link)*
7. CDC: coronavirus disease 2019 (COVID-19) – cases in the US *(external link)*
8. CDC: COVIDView *(external link)*
9. GenBank *(external link)*
10. WHO: infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed *(external link)*
11. CDC: interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 (COVID-19) pandemic *(external link)*
12. BMJ: covid-19 – PPE guidance *(external link)*
13. BMJ: covid-19 in primary care (UK) *(external link)*
14. BMJ: covid-19 – a remote assessment in primary care *(external link)*
15. BMJ Learning: Covid-19 – handwashing technique and PPE videos *(external link)*
16. WHO: coronavirus disease (COVID-19) advice for the public *(external link)*
17. Centre for Evidence-Based Medicine: what is the evidence to support the 2-metre social distancing rule to reduce COVID-19 transmission? *(external link)*
18. BMJ: facemasks for the prevention of infection in healthcare and community settings *(external link)*
19. BMJ: analysis – face masks for the public during the covid-19 crisis *(external link)*
20. Public Health England: coronavirus (COVID-19) – how to self-isolate when you travel to the UK *(external link)*
21. Public Health England: staying alert and safe (social distancing) *(external link)*





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22. Public Health England: guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19 *(external link)*

23. Public Health England: guidance for young people on shielding and protecting people most likely to become unwell if they catch coronavirus *(external link)*

24. Royal College of Paediatrics and Child Health: COVID-19 – 'shielding' guidance for children and young people *(external link)*

25. Public Health England: COVID-19 – advice for smokers and vapers *(external link)*

26. BSTI: radiology decision tool for suspected COVID-19 *(external link)*

27. BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas *(external link)*

28. WHO: public health surveillance for COVID-19 – interim guidance *(external link)*

29. CDC: coronavirus disease 2019 (COVID-19) 2020 interim case definition *(external link)*

30. PHE: COVID-19 – investigation and initial clinical management of possible cases *(external link)*

31. ECDC: case definition for coronavirus disease 2019 (COVID-19) *(external link)*

32. WHO: home care for patients with suspected or confirmed COVID-19 and management of their contacts *(external link)*

33. CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19) *(external link)*

34. Clinical frailty scale *(external link)*

35. BMJ: drug treatments for covid-19 – living systematic review and network meta-analysis *(external link)*

36. BMJ: remdesivir for severe covid-19 – a clinical practice guideline *(external link)*

37. ACOG: outpatient assessment and management for pregnant women with suspected or confirmed novel coronavirus (COVID-19) *(external link)*

38. Global coronavirus COVID-19 clinical trial tracker *(external link)*

39. WHO: off-label use of medicines for COVID-19 *(external link)*

40. RECOVERY trial *(external link)*

41. Centre for Evidence-Based Medicine: hydroxychloroquine for COVID-19 – what do the clinical trials tell us? *(external link)*



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42. Centre for Evidence-Based Medicine: lopinavir/ritonavir – a rapid review of effectiveness in COVID-19 *(external link)*

43. Centre for Evidence-Based Medicine: global COVID-19 case fatality rates *(external link)*

44. CDC: interactive serology dashboard for commercial laboratory surveys *(external link)*

45. NHS England: acute kidney injury (AKI) algorithm *(external link)*

46. WHO: coronavirus disease (COVID-19) advice for the public – when and how to use masks *(external link)*

47. Public Health England: how to make a cloth face covering *(external link)*

48. CDC: use of cloth face coverings to help slow the spread of COVID-19 (includes instructions on how to make masks) *(external link)*

49. WHO: coronavirus disease (COVID-19) travel advice *(external link)*

50. CDC: coronavirus disease 2019 (COVID-19) – travel *(external link)*

51. NaTHNac: travel health pro *(external link)*

52. Public Health England: travel advice – coronavirus (COVID-19) *(external link)*

53. Smartraveller Australia: COVID-19 *(external link)*

54. Government of Canada: coronavirus disease (COVID-19) – travel restrictions, exemptions, and advice *(external link)*

55. Ministry of Manpower Singapore: advisories on COVID-19 *(external link)*

56. CDC: coronavirus disease 2019 (COVID-19) – pets and other animals *(external link)*

57. WHO: coronavirus disease (COVID-19) pandemic *(external link)*

58. CDC: coronavirus (COVID-19) *(external link)*

59. NHS UK: coronavirus (COVID-19) *(external link)*

60. NHS UK: COVID-19 patient rehabilitation booklet *(external link)*

61. NHS UK: your COVID recovery *(external link)*





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# Key articles

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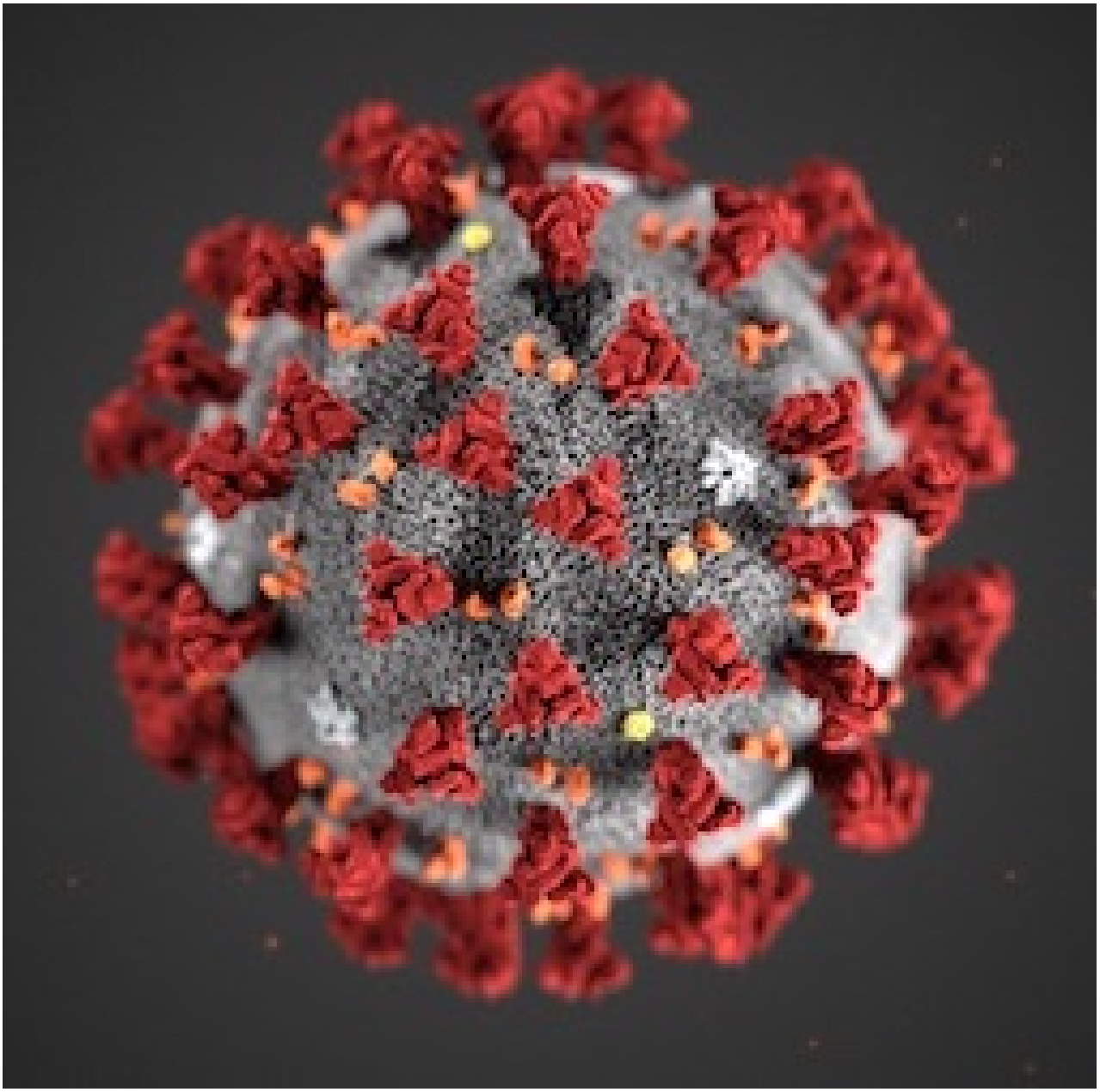

*Figure 1: Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically*

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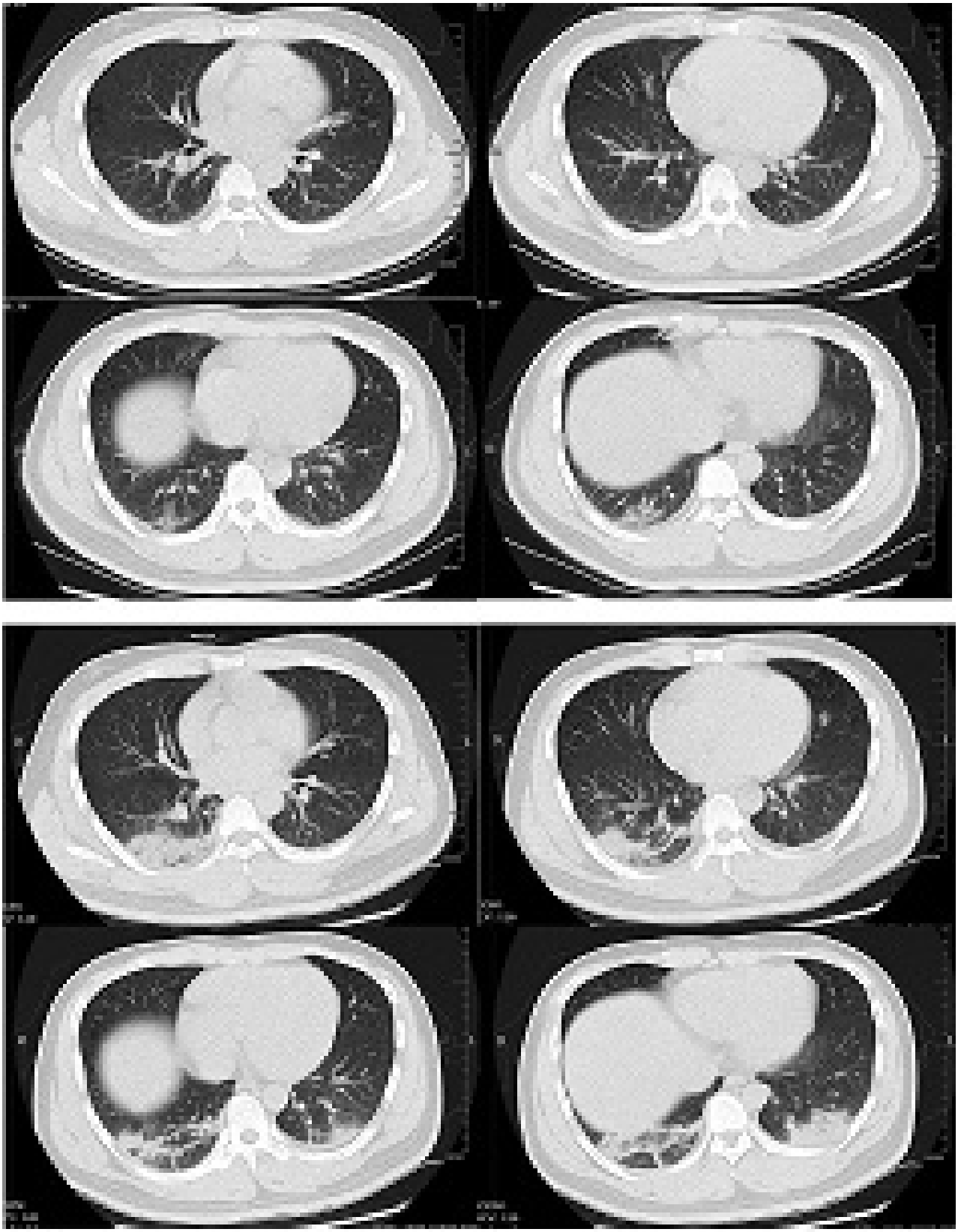

*Figure 2: Transverse CT scans from a 32-year-old man, showing ground-glass opacity and consolidation of lower lobe of right lung near the pleura on day 1 after symptom onset (top panel), and bilateral ground-glass opacity and consolidation on day 7 after symptom onset*

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

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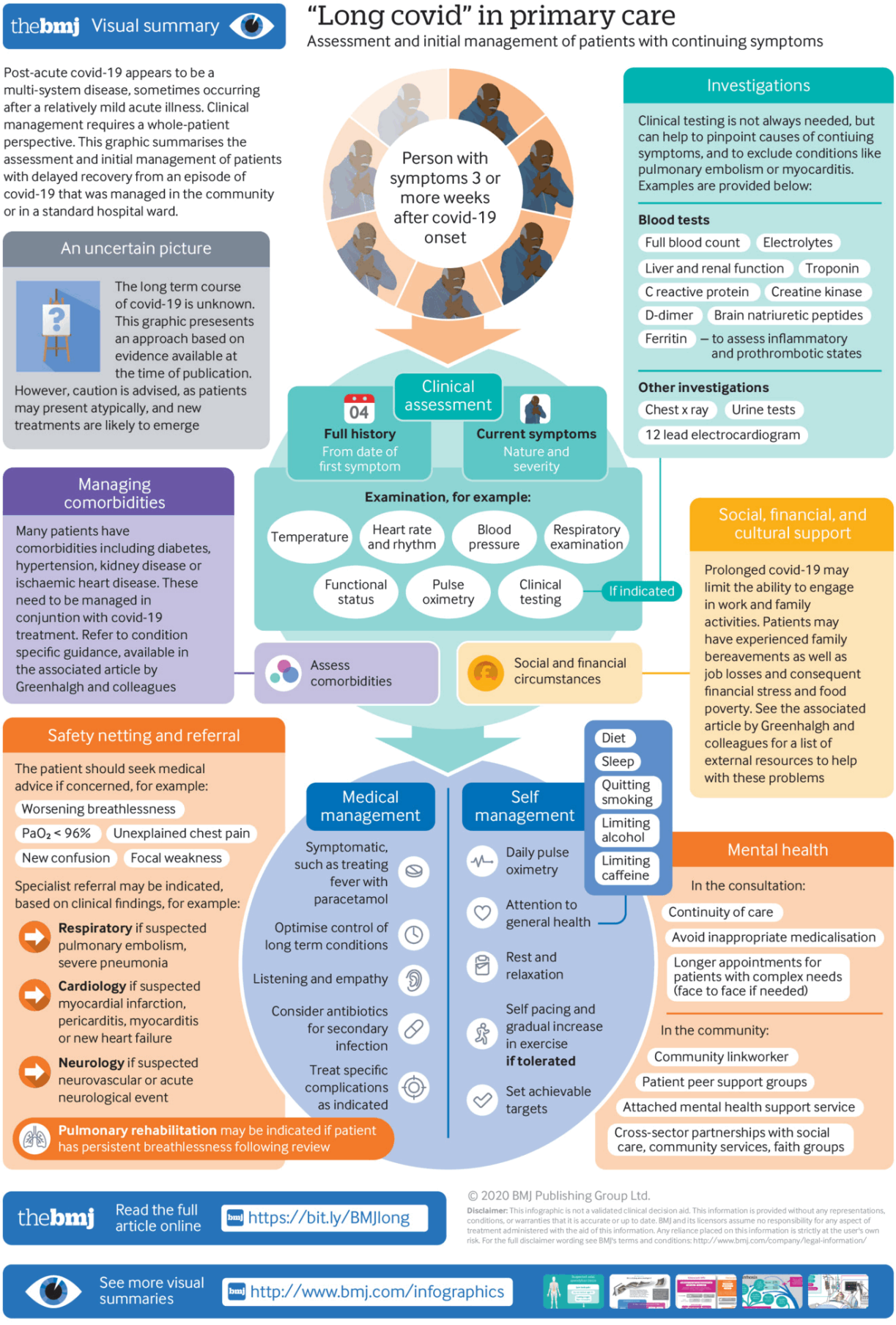


*Figure 3: "Long covid" in primary care*


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