

# BMJ Best Practice

## Coronavirus disease 2019 (COVID-19)

The right clinical information, right where it's needed



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## Summary

- ◇ 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. The condition has been given the official name of coronavirus disease 2019 (COVID-19). Clinical trials and investigations to learn more about the virus, its origin, how it affects humans, and its management are ongoing.
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## Definition

A potentially severe acute respiratory infection caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>[1]</sup> 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.<sup>[4]</sup>
- In Italy, the median age and prevalence of comorbidities was higher compared with China.<sup>[5]</sup>
- 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.<sup>[6]</sup>
- In the US, older patients (aged  $\geq 65$  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  $\geq 85$  years.<sup>[7]</sup>

### Children

- Children are less likely to be affected than adults, and account for up to 5% of confirmed cases depending on geographical location:<sup>[4] [8] [9] [10] [11] [12] [13] [14] [15]</sup>
  - 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: 1.7% (median age 9.6 years or 17.3 years in critically ill; higher in males but not statistically significant).
- Most cases are from familial clusters, or children who have a history of close contact with an infected patient.<sup>[16]</sup> Unlike adults, children do not seem to be at higher risk for severe illness based on age or sex.<sup>[17]</sup>

### 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.<sup>[18]</sup>

### Healthcare workers

- Infection rates in healthcare workers vary between countries. In the UK, 14% of healthcare workers who were screened tested positive.<sup>[19]</sup> In the Netherlands, 6% of healthcare workers who were tested

were positive for SARS-CoV-2.[20] In China, infection rates in healthcare workers ranged from 1% to 4%.[21] [22]

- 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.[23]

#### Current case counts

- [\[WHO: coronavirus disease \(COVID-19\) emergency dashboard\]](#)
- [\[WHO: coronavirus disease \(COVID-2019\) situation reports\]](#)
- [\[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.[24]
- 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.[25] [26] 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.[27]

### [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.[28] [29] [30]
- 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.[25] [26] [31] [32] Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses.[33] [34] Over 5 months after the initial outbreak, the virus is yet to be identified in an animal host.[35]

## Transmission dynamics

- Person-to-person spread occurs in community and healthcare settings, with local transmission reported in many countries around the world.
- 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.[\[30\]](#)
- It is uncertain how easily the virus spreads between people, but transmission in chains involving several links has been recognised. Available evidence indicates that human transmission occurs via close contact with respiratory droplets produced when a person exhales, sneezes, or coughs; via direct contact with infected people; or, more rarely, via contact with fomites. Airborne transmission has not been reported or confirmed; however, it may be possible during aerosol-generating procedures performed in clinical care.[\[28\]](#) [\[30\]](#) [\[36\]](#) [\[37\]](#) [\[38\]](#)
- 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.[\[30\]](#) [\[39\]](#) However, the  $R_0$  may actually be lower in light of social distancing measures that have been instituted.[\[40\]](#)
- 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).[\[41\]](#) 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.[\[42\]](#)
- 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.[\[43\]](#) 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.[\[44\]](#) [\[45\]](#) [\[46\]](#) [\[47\]](#) [\[48\]](#) [\[49\]](#) [\[50\]](#) [\[51\]](#) [\[52\]](#) The 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.[\[51\]](#)
- Nosocomial transmission in healthcare workers and patients has been reported in 44% of patients.[\[53\]](#) 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.[\[54\]](#)
- Widespread transmission has been reported in long-term care facilities, homeless shelters, meat processing facilities, and prisons, and on cruise ships (19% of 3700 passengers and crew were infected aboard the Diamond Princess).[\[55\]](#) [\[56\]](#) [\[57\]](#) [\[58\]](#) [\[59\]](#) [\[60\]](#) [\[61\]](#) There is a lack of evidence for transmission in the school setting.[\[62\]](#)
- Clusters of cases originating from family gatherings, weddings, choir practices, fitness classes, religious gatherings, and churches have been reported.[\[63\]](#) [\[64\]](#) [\[65\]](#) [\[66\]](#) [\[67\]](#) [\[68\]](#) 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.[\[69\]](#)
- The secondary attack rate among all close contacts is approximately 0.45% to 0.7%.[\[37\]](#) [\[70\]](#) The secondary attack rate among household members is higher and ranges from 4.6% to 30%.[\[37\]](#) [\[70\]](#) [\[71\]](#) [\[72\]](#) The secondary attack rate in children is lower compared with adults, and 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.[72]

### 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]
- Presymptomatic transmission has been reported in 12.6% of cases in China.[73] 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.[74]
- 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.[75]

### Asymptomatic transmission

- An asymptomatic case is a laboratory-confirmed case who does not develop symptoms. 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).[76] [77] [78] [79] [80] [81] [82] According to the World Health Organization, asymptomatic individuals are much less likely to transmit the virus than those who develop symptoms.[83] 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.[84] The majority of asymptomatically infected people remained asymptomatic throughout the course of infection in one cohort study.[85] Another small retrospective cohort study found no evidence of asymptomatic transmission from nine carriers to any close contacts over an average of 85 days.[86]
- Estimating the prevalence of asymptomatic cases in the population is difficult. 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.[87] However, a Japanese study of citizens evacuated from Wuhan City estimates the rate to be closer to 31%.[88] Early data from an isolated village of 3000 people in Italy estimates the figure to be higher at 50% to 75%.[89] Other studies ranged from 4% to 80%.[90] A narrative review of 16 cohorts found that the asymptomatic infection rate could be as high as 40% to 45%.[91]
- 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.[92] 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.[93]
- Asymptomatic (or paucisymptomatic) transmission has been reported in family clusters.[94]
- The proportion of asymptomatic cases in children is thought to be significant, and children may play a role in community spread.[95] 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.[\[96\]](#)

### Superspreading events

- 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.[\[97\]](#)
- 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.[\[98\]](#) [\[99\]](#)
- 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.[\[98\]](#)

### Perinatal transmission

- There is currently no evidence of vertical transmission, although there have been cases where it is suspected but not confirmed.[\[100\]](#) Neonatal infection is uncommon; in one systematic review, 4% of neonates had confirmed infection postnatally. The rate of infection is not greater when the baby is born vaginally, breastfed, or allowed contact with the mother.[\[101\]](#) Viral fragments have been detected in breast milk, but the significance of this is unknown.[\[102\]](#) [\[103\]](#) [\[104\]](#)

### 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.[\[105\]](#) [\[106\]](#) High viral load at baseline may be associated with more severe disease and risk of disease progression.[\[107\]](#)
- 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.[\[108\]](#)
- 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.[\[109\]](#) [\[110\]](#) [\[111\]](#) [\[112\]](#) [\[113\]](#) [\[114\]](#) Viral shedding continued until death in non-survivors.[\[109\]](#)
- Duration of viral shedding was longer in symptomatic patients compared with asymptomatic patients (25.2 days versus 22.6 days).[\[115\]](#) The median duration of shedding was lower in mild illness compared with severe illness (14 days versus 21 days).[\[116\]](#)
- Viral shedding in stool has been detected in 41% of patients.[\[117\]](#) 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.[\[116\]](#)
- 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.[\[118\]](#)
- There is no convincing evidence that duration of viral shedding correlates with duration of infectivity.[\[119\]](#)



## 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.[26] [120] 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.[121] 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.[122] [123]

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.[124] 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.[125]

The virus uses the host transmembrane protease serine 2 (TMPRSS2) for S protein priming and fusion of viral and host cell membranes.[126] A furin-like cleavage site has been identified in the spike protein of the virus; this does not exist in other SARS-like coronaviruses.[127]

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.[128] [129] [130] [131] [132] [133]

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.[134]

There is a hypothesis that COVID-19 is a disease of the endothelium.[135] [136] [137] 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.[138]

## 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 ( $\text{SpO}_2$ )  $\geq 90\%$  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:  $\geq 60$  breaths/minute
  - 2-11 months of age:  $\geq 50$  breaths/minute
  - 1-5 years of age:  $\geq 40$  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
  - $\text{SpO}_2 < 90\%$  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  $\text{SpO}_2 < 90\%$
  - Severe respiratory distress (e.g., fast breathing, grunting, very severe chest indrawing)
  - General danger sign
  - 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<sup>[3]</sup>

#### 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 ( $\text{SpO}_2$ )  $>93\%$  on room air at sea level.

#### Severe illness

- People who have respiratory frequency  $>30$  breaths per minute,  $\text{SpO}_2 \leq 93\%$  on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ )  $<300$ , or lung infiltrates  $>50\%$ .

#### Critical illness

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

# Primary prevention

## Infection prevention and control for healthcare professionals

- Immediately isolate all suspected cases in an area that is separate from other patients. Ask the patient to wear a mask, and ensure there is at least 1 metre (3 feet) between patients.[269] Some countries recommend larger distances, so local guidance should be consulted.
- Implement standard precautions at all times:[269]
  - Practice hand and respiratory hygiene
  - Offer a medical mask to patients who can tolerate one
  - Wear personal protective equipment
  - Practice safe waste management, environmental cleaning, and sterilisation of patient care equipment and linen.
- Implement additional contact and droplet precautions until the patient is asymptomatic:[269]
  - Place patients in adequately ventilated single rooms; when single rooms are not available, place all suspected cases together in the same ward
  - 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
  - Consider limiting the number of healthcare workers, family members, and visitors in contact with the patient, ensuring optimal patient care and psychosocial support for the patient
  - Consider placing patients in negative pressure rooms, if available.
- Implement airborne precautions when performing aerosol-generating procedures. Some countries and organisations recommend airborne precautions for any situation involving the care of a COVID-19 patient.[269]
- All specimens collected for laboratory investigations should be regarded as potentially infectious.[269]
- It is important to clean and disinfect inanimate surfaces in the surgery or hospital. Follow local cleaning and disinfection procedures.[270]
- 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.[271] 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.[272]
- Detailed infection prevention and control guidance is available:
  - [\[WHO: infection prevention and control during health care when COVID-19 is suspected\]](#)
  - [\[CDC: interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 \(COVID-19\) pandemic\]](#)
  - [\[CDC: strategies to optimize the supply of PPE and equipment\]](#)
  - [\[BMJ: covid-19 – PPE guidance\]](#)

## 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.[273] 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

- People should be advised to:[\[274\]](#) [\[275\]](#)
  - 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[\[276\]](#)
  - 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.[\[277\]](#) 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.[\[83\]](#) [\[278\]](#) 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.[\[279\]](#)
- 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.[\[83\]](#)
- 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.[\[280\]](#)
- 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.[83]

- 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 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.[83] 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.[281] 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.[282]
- [BMJ: facemasks for the prevention of infection in healthcare and community settings]
- [BMJ: analysis – face masks for the public during the covid-19 crisis]

### 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.[283] 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.[284]
- 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).[285] The psychosocial effects of enforced quarantine may have long-lasting repercussions.[286] [287] 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.[288]
- Travellers who arrive in the UK are required to self-isolate for 14 days. [PHE: 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.[289] [290]
- 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.[291]
- [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:[176]
  - 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.
- These groups should continue to take precautions, but can now leave their home if they wish with strict social distancing (i.e., keeping 2 metres [6 feet] apart from others). Outdoor time can be spent with members of their own household, or one person from another household (ideally the same person each time). Shielding is a personal decision and is not mandatory.
- Visits from people who provide essential support should continue provided these people do not have symptoms and follow hand hygiene measures.
- Shielding advice for children and young adults is available; children can be divided into group A (conditions that require shielding) or group B (conditions that require discussion between the clinician and the child and their family/carer to establish whether shielding is necessary).[292]
- Consult local health authorities for more guidance as recommendations, procedures, and resources differ between countries.
- [\[Public Health England: guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19\]](#)
- [\[Royal College of Paediatrics and Child Health: COVID-19 – 'shielding' guidance for children and young people\]](#)

## Vaccines

- There is currently no vaccine available. Vaccines are in development, but it may take at least 12 to 18 months before one is available. 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.[293]
- 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).[294] [295]
- Results from preliminary animal and human studies are beginning to emerge, but scientists urge caution over the results.[296]
- 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 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. A phase 2 trial is ongoing.[297]
- 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.[298] Despite this, researchers are moving to human trials.
- 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.[299]

- 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. Animal studies in mice have been completed, but testing in other animals such as hamsters, ferrets, and non-human primates has been skipped in order to expedite the vaccine development process. Results from a phase 1 trial indicated that all 45 healthy adults (ages 18-55 years) seroconverted by day 15 after the first dose, according to a press release issued by the manufacturer. Of the cohort of 15 patients who received the highest dose (250 micrograms), 20% of participants experienced grade adverse events following the second dose (the press release does not say what these were). Of the two cohorts who received the 25 microgram and 100 microgram doses, only one patient experienced a grade 3 adverse event (erythema at injection site). No grade 4 adverse events were reported in this small cohort. The study did not include people with underlying conditions.[300] mRNA-1273 has been granted fast-track designation by the US Food and Drug Administration, and phase 2 trials are expected to start soon.

#### Immunity passports

- Some governments are discussing or implementing certifications for people who have contracted and recovered from COVID-19 based on antibody tests (sometimes called 'immunity passports'). Possession of a passport would allow people to have a greater range of privileges (e.g., work, education, travel). However, the WHO does not support these certifications as there is currently no evidence that people who have recovered from infection and have antibodies are protected from reinfection.[301] 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.[302]

#### Smoking cessation

- Past or current smokers have nearly double the risk for severe disease, and smoking cessation should be encouraged.[205] The WHO recommends that tobacco users stop using tobacco given the well-established harms associated with tobacco use and second-hand smoke exposure.[207] Public Health England also recommends stopping smoking. [PHE: COVID-19 – advice for smokers and vapers]

## Screening

### Management of contacts

People who may have been exposed to individuals with suspected COVID-19 (including healthcare workers) should be advised to monitor their health for 14 days from the last day of possible contact. A contact is a person who is involved in any of the following from 2 days before, and up to 14 days after, the onset of symptoms in the patient:[440]

- Face-to-face contact with a COVID-19 patient within 1 metre (3 feet) for more than 15 minutes
- Providing direct care for patients with COVID-19 without using proper personal protective equipment
- Staying in the same close environment (e.g., workplace, classroom, household, gathering) as a COVID-19 patient for any amount of time
- Travelling in close proximity within 1 metre (3 feet) with a COVID-19 patient in any kind of conveyance
- Other situations as indicated by local risk assessments.

If a contact develops symptoms, they should notify the receiving facility, wear a medical mask while travelling to seek care, avoid taking public transport (e.g., call an ambulance or use a private vehicle), perform respiratory and hand hygiene, sit as far away from others as possible in transit, and clean any contaminated surfaces.

## 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.<sup>[441]</sup> 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.<sup>[442]</sup>

## 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.<sup>[443]</sup>

## 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.

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.<sup>[2]</sup> 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.

### 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:<sup>[139]</sup>

- Patients with acute respiratory illness (i.e., fever and at least one sign/symptom of respiratory disease such as cough or shortness of breath) and a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset.

- Patients with any acute respiratory illness if they have been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset.

See Diagnostic criteria section for case definitions.

## 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.[29] 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
- Anorexia
- Sputum production
- Chest tightness
- Gastrointestinal symptoms
- Sore throat
- Dizziness
- Headache
- Neurological symptoms
- Cutaneous symptoms
- Rhinorrhoea/nasal congestion
- Chest pain
- Conjunctivitis
- Haemoptysis.

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.[303] 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.[146]

In terms of severity:[4]

- 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.[304]

There is anecdotal evidence suggesting that the course of the disease may be protracted, with ever-changing symptoms and periods of feeling better interspersed with periods of relapse in some patients (similar to a post-viral fatigue syndrome), even in those with mild disease.[305]

#### Pregnant women

- The clinical characteristics in pregnant women are similar to those reported for non-pregnant adults.[306] 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.[307] [308] [309] [310]

#### 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.[311]
- Co-infections may be associated with protracted respiratory symptoms, prolonged intensive care stay, morbidity, and mortality if not detected and treated early.[312]
- Patients with influenza co-infection showed similar clinical characteristics to patients with COVID-19 only.[313] [314]

## 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:[315]

- 37% of children present with mild illness
- 45% of children present with moderate illness
- 3% of children present with severe illness



- 0.6% of children present with critical illness
- 16% 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.[316] Febrile seizures have been reported rarely.[12] The clinical manifestations in children under 5 years of age appear to be milder compared with those of influenza A infection.[317]

Severe disease has been reported rarely in children.[316] [318] 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.[319] 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.[316] [320] [321] [322]

Co-infections may be more common in children.[323] 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* .[11] [12]

## 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.

## Pulse oximetry

Pulse oximetry may reveal low oxygen saturation ( $\text{SpO}_2 < 90\%$ ). 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.[324]

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.[325]

## 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.[146] [326] [327] [328] Laboratory abnormalities – in particular, lymphopenia, leukocyte abnormalities, and other markers of systemic inflammation – are less common in children.[316] [329] [330] 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.[331]

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.[332] 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.[333]

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.[334]

- 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 aerosolisation when collecting lower respiratory specimens.

- Also consider collecting additional clinical specimens (e.g., blood, stool, urine).

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%).<sup>[335]</sup>

False-negative rates of between 2% and 29% have been reported.<sup>[335]</sup> 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.<sup>[336]</sup>

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.<sup>[334]</sup> Guidelines recommend that two consecutive negative tests (at least one day apart) are required to exclude COVID-19; however, 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.<sup>[337]</sup>

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.<sup>[2] [338]</sup>

## Serological testing

Serological testing is becoming increasingly available for use; however, while rapid antibody detection kits have been approved in Europe and the US 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.<sup>[339]</sup>

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, IgM and IgG, or total antibody. The test's positive predictive value should be high (99.5% or greater), and 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. Serological tests should not be used to make decisions about people returning to their workplace.<sup>[340]</sup>

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.<sup>[341] [342]</sup>

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.<sup>[343]</sup>

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.[28] [29] [344] 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.[345]

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 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.[346]

[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.[347]

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.[348]

Abnormal chest CT findings have been reported in up to 97% of COVID-19 patients in one meta-analysis of 50,466 hospitalised patients.[349] Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[350] CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients.[79] [351] More than half of patients with asymptomatic disease present with CT abnormalities.[331] Some patients may present with a normal chest finding despite a positive RT-PCR.[352] 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.[353]

#### 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.[354]
- 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.[354]
- 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.[355]
- Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity and, less frequently, areas of consolidation. Abnormalities are more

common in the lower lobes and are predominantly unilateral. Pleural effusion is rare.[356] Children may have signs of pneumonia on chest imaging despite having minimal or no symptoms.[323]

#### Atypical features

- Pulmonary vascular enlargement, interlobular or intralobular septal thickening, adjacent pleural thickening, air bronchograms, subpleural lines, crazy-paving pattern, bronchus distortion, bronchiectasis, vacuolar retraction sign, and halo sign are atypical features. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have also been reported rarely.[354]

The WHO recommends chest imaging in the following scenarios:[345]

- 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.[357] [358] [359]

#### 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.[360]

#### 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.[345] 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.[361] May be used in pregnant women and children.[362] [363]

- [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas]

## Risk factors

### Strong

#### residence in/travel to location reporting community transmission

- Diagnosis should be suspected in patients with acute respiratory illness (i.e., fever and at least one sign/symptom of respiratory disease such as cough or shortness of breath) and a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset.[139]

#### close contact with a confirmed case

- Diagnosis should be suspected in patients with any acute respiratory illness if they have been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset.[139]

### older age

- Older age is a risk factor for infection.[140] 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.[141] People aged 65 years and older are at higher risk for severe illness.[142] 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]

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

- Widespread transmission has been reported in long-term care facilities.[55] People who live in a nursing home or long-term care facility are at higher risk for severe illness.[142] 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.[143] More than one third of care homes in England have had cases.[144] 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 SARS-CoV-2, and of these, 43% were asymptomatic and 18% had atypical symptoms.[145]

### male sex

- Male sex is a risk factor for infection.[140] 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%).[141] Male sex is also a risk factor for severe disease, disease progression, need for mechanical ventilation, and increased mortality.[4] [146] [147] It has been hypothesised that this may be due to the presence of androgens, or a lower level of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies compared with females; however, further research is required.[148] [149]



## ethnicity

- People from Black, Asian, and minority ethnic (BAME) groups in England are at a higher risk of infection and worse outcomes, including an increased risk of mortality, compared with the general population. This may be partially explained by the geographical distribution of COVID-19 in England, deprivation, and occupational exposure. The average age of patients from ethnic minorities was significantly lower than that of White patients.[150] 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%).[141] There is also evidence from the US that shows non-uniform deaths across BAME groups.[151] Data from a New York study found that 62% of critically ill patients admitted to two hospitals were Hispanic or Latin, 32% were White, 19% were Black, and 3% were Asian.[152] 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.[153]

## presence of comorbidities

- People with comorbidities are at higher risk for severe illness and mortality.[154] The most prevalent comorbidities in adults with COVID-19 are hypertension, cardiovascular disease, diabetes, chronic respiratory disease, malignancy, chronic kidney disease, cerebrovascular disease, and obesity.[155] [156] [157] 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.[158] It has been estimated that approximately 45% of adults in the US are at risk for complications from COVID-19 because of the presence of comorbidities. The risk is higher in people ages 80 years and older.[159]
- 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.[10] 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.[11]

## hypertension

- Hypertension is associated with increased poor composite outcome, including mortality, severe COVID-19, acute respiratory distress syndrome, need for intensive care admission, and disease progression in patients with COVID-19.[160] 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.[161]

## cardiovascular disease

- Underlying or previous history of cardiovascular disease is associated with severe disease and poor prognosis. Previous cardiovascular disease and hypertension are associated with higher odds of in-hospital mortality, as is acute cardiac injury.[162] Cardiovascular disease is associated with a 3-fold increased odds of severe infection, and an 11-fold increase in all-cause mortality.[163]

## diabetes

- The pooled prevalence of diabetes in COVID-19 patients is approximately 10%. Prevalence is significantly higher in older patients and patients with severe COVID-19.[164] [165] [166] Diabetes is associated with increased risk of mortality, severe disease, disease progression, and acute respiratory distress syndrome.[167] Patients with diabetes have a 2-fold higher risk of developing severe disease, and a 2-fold higher risk of mortality.[165] Risk factors for poor prognosis and higher mortality include older age, elevated C-reactive protein, and insulin use.[168] One third of all deaths in hospitalised patients with COVID-19 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.[169] Patients with poorly controlled hyperglycaemia have an increased risk of disease severity and mortality.[170] [171] Body mass index is positively and independently associated with tracheal intubation and/or death within 7 days in patients with diabetes.[172] Patients with newly diagnosed diabetes have a higher risk of all-cause mortality compared with patients with known diabetes, hyperglycaemia, or normal glucose.[173]

## chronic respiratory disease

- There is no clear evidence that people with asthma or chronic obstructive pulmonary disease are at higher risk of infection.[174] [175] However, patients with respiratory diseases such as cystic fibrosis, severe asthma, chronic obstructive pulmonary disease, interstitial lung disease, or pulmonary sarcoidosis may have an increased risk for severe disease, poor prognosis, and worse outcomes.[176] [177] [178] Chronic obstructive pulmonary disease is associated with a 5-fold increased risk of severe COVID-19 infection.[179] There is no statistically significant association between asthma and a higher risk of mortality in patients with COVID-19, although patients with asthma may have a higher risk for severe disease.[180] [181] Asthma has been associated with a longer intubation time in those who require mechanical ventilation, especially in patients younger than 65 years.[182] There are no data on whether paediatric respiratory diseases (including childhood asthma) are risk factors for infection or severity.[183]

## chronic kidney disease

- 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%).[141]

## malignancy

- Patients with cancer are at a higher risk of infection, likely due to immunosuppressive treatments and/or recurrent hospital visits.[184] Patients with cancer are 76% more likely to get severe disease compared with those without cancer.[185] 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.[186] [187] Patients who underwent cancer surgery had higher mortality rates.[188] 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.[189] [190] [191] However, a subgroup analysis of patients aged 65 years and older found that all-cause mortality was comparable to patients without cancer.[187] 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.[192] 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.[193]

## cerebrovascular disease

- Patients with a history of stroke are at increased risk of severe disease and poor outcomes, including need for intensive care unit admission and mechanical ventilation, and increased risk of mortality compared with those without a history of stroke.[194]

## obesity

- 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%).[141] Data from France estimates that the prevalence of obesity is 1.35 times higher in patients with severe COVID-19 compared with the general population.[195] Obesity is a risk factor for severe disease, respiratory failure leading to invasive mechanical ventilation, and mortality.[196] [197] Obesity may be a significant risk factor for the development of severe COVID-19 or mortality in younger people <60 years of age.[198] [199] [200] [201] Increased body mass index is a significant risk factor for severe disease in pregnant women.[202] 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.[203]

## smoking

- Current data suggest smoking is associated with disease severity and mortality in hospitalised COVID-19 patients.[204] Smokers have 1.91 times the odds of progression in COVID-19 severity compared with people who never smoked.[205] This may be due to increased airway expression of the angiotensin-converting enzyme-2 receptor in smokers.[206] 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.[207]

## chronic liver disease

- Patients with pre-existing liver disease (e.g., cirrhosis) are at increased risk of hospitalisation, poor outcomes, and mortality.[208] [209] [210] 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.[211]

## metabolic dysfunction-associated fatty liver disease

- Patients with severe COVID-19 are 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.[212] MAFLD is associated with a 4- to 6-fold increase in severity of COVID-19.[213] 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.[214] [215]

## organ transplant

- 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.[216] [217] [218] [219] [220] [221]

## surgery

- Surgical mortality and complications are higher in patients with COVID-19 compared with patients without COVID-19.[222] 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.[223] Postoperative pulmonary complications occur in half of patients with perioperative SARS-CoV-2 infection, and are associated with higher mortality, particularly in men and those aged 70 years and over.[224]

## air pollution

- Evidence suggests that there may be an association between long-term exposure to ambient air pollution and COVID-19.[225] [226] [227] [228] 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.[229] 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.[230] 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<sup>3</sup> in fine particulate matter is associated with an 8% increase in the COVID-19 death rate.[231]

## Weak

### climate and latitude

- Distribution of community outbreaks along restricted latitude, temperature, and humidity measurements are consistent with the behaviour of a seasonal respiratory virus.[232] Evidence suggests that cold and dry conditions increase transmission, and warm and humid conditions reduce the rate of infections.[233] [234] [235] [236] However, there is other evidence that suggests ambient temperature has no significant impact on transmission, especially during the pandemic stage of an emerging pathogen.[237] [238] [239] 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.[240]

### 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%).[141]

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

- There is concern that people on these drugs may be at increased risk of COVID-19 or more severe disease due to upregulation of angiotensin-converting enzyme-2 (ACE2) receptor expression.[241] Some studies have shown that there is no association between the use of these drugs and testing positive for COVID-19.[242] [243] However, a meta-analysis of over 24,000 patients found that use of these drugs is not associated with a higher risk of in-hospital death and/or severe illness among hypertensive patients with COVID-19 infection.[244] In a nested case-control analysis of nearly

500,000 patients with hypertension, use of these drugs was not significantly associated with COVID-19 diagnosis compared with use of other antihypertensive medications.[245] 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.[246] Professional societies recommend that patients who are already on these drugs continue to take them.[247] [248] [249]

## immunosuppression

- Limited data suggest that immunosuppressed patients are not at increased risk of infection or severe illness; however, further research is required as there is concern about the risk of infection in these patients.[250] [251] [252] [253] [254] [255] 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.[256] Glucocorticoid exposure of  $\geq 10$  mg/day (prednisolone) has been associated with a higher odds of hospitalisation in patients with rheumatological disease.[257] HIV co-infection does not significantly impact presentation, hospital course, or outcomes of patients when compared with non-matched non-HIV patients.[258]

## autoimmune disease

- Autoimmune disease does not appear to be associated with a higher risk of infection.[259] [260] It has been associated with a slightly increased risk of disease severity and mortality; however, this was not statistically significant.[261] Risk of mortality appears to be associated with older age and the presence of comorbidities even in patients with autoimmune disease, rather than the autoimmune disease itself or use of immunosuppressive medications.[262] Further research is required as there is concern about the risk of infection in these patients.

## blood group A#

- There is emerging evidence that people with blood group A may be at higher risk of severe COVID-19 and hospitalisation, and blood group O may be associated with a protective effect.[263] [264] 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.[265]

## 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.[266] [267] [268]

# History & examination factors

## Key diagnostic factors

### fever (common)

- Reported in approximately 78% of patients.[364] 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.[365] 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.[366]

### cough (common)

- Reported in approximately 57% of patients.[364] 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.[364] 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.[28] [29] [367] It is less common in children, but the most common sign in neonates.[316] May last weeks after initial onset of symptoms. Wheeze has been reported in 17% of patients.[364]

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

- The pooled prevalence of olfactory dysfunction (anosmia/hyposmia) is 53%, with a pooled prevalence of 44% for gustatory dysfunction (ageusia/dysgeusia).[368] Prevalence appears to be higher in European studies; 87% of patients self-reported loss of smell and 56% reported taste dysfunction in one study.[369]
- Initial findings from the American Academy of Otolaryngology - Head and Neck Surgery's COVID-19 anosmia reporting tool found that 73% of patients reported anosmia prior to diagnosis, and it was the initial symptom in 26.6% of patients.[370]
- There is anecdotal evidence that altered sense of smell/taste may be an early symptom of COVID-19 before the onset of other symptoms, or may be the only symptom in patients with mild to moderate illness.[371]
- The UK government now includes altered sense of taste/smell in the general clinical case definition, and recommends that patients self-isolate if they develop an altered sense of smell/taste. However, the current evidence base is of poor quality due to the mainly retrospective and cross-sectional nature of studies available.[372] [373]

## **Other diagnostic factors**

### **fatigue (common)**

- Reported in approximately 31% of patients.[364] 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.[364] Prevalence has been higher in some case series.

### **anorexia (common)**

- Reported in approximately 22.7% of patients.[327] Prevalence has been higher in some case series.

### **sputum production/expectoration (common)**

- Reported in approximately 22.7% of patients.[327] Prevalence has been higher in some case series.

### **chest tightness (common)**

- Reported in approximately 22.9% of patients.[327] Prevalence has been higher in some case series.

### **sore throat (common)**

- Reported in approximately 12% of patients.[364] Usually presents early in the clinical course.



**gastrointestinal symptoms (uncommon)**

- Diarrhoea has been reported in approximately 10% of patients, nausea in 6%, vomiting in 4%, and abdominal pain in 4%.[\[364\]](#) The pooled prevalence of gastrointestinal symptoms is 15%, and patients with severe illness have a higher prevalence. Around 10% of patients present with gastrointestinal symptoms alone.[\[374\]](#) Gastrointestinal symptoms are more prevalent outside of China.[\[375\]](#)
- 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.[\[376\]](#)
- Haematochezia has been reported.[\[377\]](#)

**dizziness (uncommon)**

- Reported in approximately 11% of patients.[\[364\]](#)

**headache (uncommon)**

- Reported in approximately 13% of patients.[\[364\]](#)

**neurological symptoms (uncommon)**

- Confusion has been reported in approximately 11% of patients.[\[364\]](#) Prevalence of confusion/delirium and agitation is high (65% and 69%, respectively) in patients in the intensive care unit.[\[378\]](#) Delirium is associated with an increased risk of mortality, and rapid onset may indicate clinical deterioration.[\[379\]](#) Anxiety, depression, and sleep problems have also been reported.[\[29\]](#)

**cutaneous symptoms (uncommon)**

- Reported in 7.8% of hospitalised adults in one observational cross-sectional study in Italy.[\[380\]](#)
- 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.[\[381\]](#) [\[382\]](#) [\[383\]](#) [\[384\]](#) [\[385\]](#) [\[386\]](#) [\[387\]](#) [\[388\]](#) [\[389\]](#)
- Chilblains, particularly on the toes or foot, are an emerging symptom, especially in younger patients (including children) who lack a history of chilblains, Raynaud's phenomenon, or collagen vascular diseases (e.g., systemic lupus erythematosus).[\[390\]](#) [\[391\]](#) [\[392\]](#) Current evidence indicates that chilblain-like acral skin lesions are not a sign of COVID-19 in otherwise asymptomatic people.[\[393\]](#)
- 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.[\[394\]](#)
- 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.[\[364\]](#)

**chest pain (uncommon)**

- Reported in approximately 7% of patients.[\[364\]](#) May indicate pneumonia.

**conjunctivitis (uncommon)**

- Reported in approximately 2% of patients.[364] Appears to be more frequent in patients with severe illness.[395] May be the only presenting symptom in some patients.[396] Ophthalmalgia and photophobia have also been reported.[364]

**haemoptysis (uncommon)**

- Reported in approximately 2% of patients.[364] May be a symptom of pulmonary embolism.[397]

**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.

# Diagnostic tests

## 1st test to order

Test	Result
<b>pulse oximetry</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>Recommended in patients with respiratory distress and cyanosis.</li> <li>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.<a href="#">[324]</a></li> </ul>	<b>may show low oxygen saturation (SpO<sub>2</sub> &lt;90%)</b>
<b>ABG</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness as indicated to detect hypercarbia or acidosis.</li> <li>Recommended in patients with respiratory distress and cyanosis who have low oxygen saturation (SpO<sub>2</sub> &lt;90%).</li> </ul>	<b>may show low partial oxygen pressure</b>
<b>FBC</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>Lymphopenia, leukocytosis, and thrombocytopenia are associated with severe disease; therefore, they may be useful as biomarkers for predicting disease progression.<a href="#">[398]</a></li> <li>High neutrophil-to-lymphocyte ratio is a useful marker for indicating risk for severe illness and poor prognosis.<a href="#">[399]</a> <a href="#">[400]</a></li> <li>Absolute counts of major lymphocyte subsets, particularly CD4+ and CD8+ T-cell counts, are significantly decreased in patients with severe disease.<a href="#">[401]</a></li> <li>Late-phase thrombocytopenia (i.e., occurring 3 weeks or more after symptom onset) has been reported but is uncommon.<a href="#">[402]</a></li> </ul>	<b>lymphopenia; leukocytosis; leukopenia; thrombocytopenia; decreased haemoglobin; decreased eosinophils#</b>
<b>comprehensive metabolic panel</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>The most common laboratory abnormalities in patients hospitalised with pneumonia include elevated liver transaminases. Other abnormalities include decreased albumin and renal impairment.<a href="#">[28]</a> <a href="#">[29]</a></li> <li>Elevated liver transaminases increase in severe disease; therefore, they may be useful as biomarkers for predicting disease progression.<a href="#">[403]</a></li> <li>Serum urea and creatinine levels increase in severe disease; therefore, they may be useful as biomarkers for predicting disease progression.<a href="#">[398]</a></li> <li>Hypoalbuminaemia is associated with severe disease and may be useful as a biomarker for predicting disease progression.<a href="#">[404]</a></li> <li>Hypokalaemia has been reported in 54% of patients.<a href="#">[405]</a></li> </ul>	<b>elevated liver transaminases; decreased albumin; renal impairment; hypokalaemia</b>
<b>blood glucose level</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> </ul>	<b>variable</b>

Test	Result
<ul style="list-style-type: none"> <li>Uncontrolled hyperglycaemia has been shown to worsen prognosis in all patients, not only patients with diabetes.[406] [407] [408]</li> <li>.</li> </ul>	
<b>coagulation screen</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>The most common abnormalities are elevated D-dimer and fibrinogen, and prolonged prothrombin time.[28] [29] [367] [409]</li> <li>D-dimer levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[398]</li> <li>Patients with very high D-dimer levels have an increased risk of thrombosis.[410] [411]</li> </ul>	<b>elevated D-dimer; prolonged prothrombin time; elevated fibrinogen</b>
<b>serum C-reactive protein</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[398] [412]</li> </ul>	<b>may be elevated</b>
<b>serum erythrocyte sedimentation rate</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>Commonly elevated in patients with COVID-19.[328]</li> </ul>	<b>may be elevated</b>
<b>serum lactate dehydrogenase</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[398]</li> <li>May be more common in patients with COVID-19 compared with other types of pneumonia.[355]</li> </ul>	<b>may be elevated</b>
<b>serum interleukin-6 level</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>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.[398] [413] It is less likely to be elevated in children.[414]</li> </ul>	<b>may be elevated</b>
<b>cardiac biomarkers</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>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.[398]</li> <li>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.[415] [416]</li> <li>Creatine kinase-myocardial band has been found to be elevated in mild disease in children.[330]</li> </ul>	<b>may be elevated</b>
<b>serum procalcitonin</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[417]</li> <li>May be elevated in patients with secondary bacterial infection.[28] [29] May be more common in children.[323]</li> <li>There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about the use of antibiotics.[418]</li> </ul>	<b>may be elevated</b>

Test	Result
<ul style="list-style-type: none"> <li>However, it may be helpful in limiting overuse of antibiotics in patients with COVID-19-related pneumonia.[419]</li> </ul>	
<b>serum ferritin level</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>May indicate development of cytokine release syndrome.[420]</li> </ul>	may be elevated
<b>serum amyloid A level</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[398]</li> </ul>	may be elevated
<b>serum creatine kinase</b> <ul style="list-style-type: none"> <li>Order in patients with severe illness.</li> <li>Elevated creatine kinase has been reported in 13% to 33% of patients.[28] [29]</li> <li>Indicates muscle or myocardium injury.</li> </ul>	may be elevated
<b>blood and sputum cultures</b> <ul style="list-style-type: none"> <li>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]</li> <li>Testing is most useful when there is concern for multidrug-resistant pathogens.[419]</li> <li>Specimens should be collected prior to starting empirical antimicrobials if possible.</li> </ul>	negative for bacterial infection
<b>real-time reverse transcription polymerase chain reaction (RT-PCR)</b> <ul style="list-style-type: none"> <li>Molecular testing is required to confirm the diagnosis. Nucleic acid sequencing may be required to confirm the diagnosis.[334] Priorities for testing depend on local guidelines and available resources.</li> <li>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%.[421]</li> <li>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 aerosolisation when collecting lower respiratory specimens.[334]</li> <li>There are little data available on the rates of false-positive and false-negative results for the various RT-PCR tests available; however, both have been reported. 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.[334]</li> <li>Many tests are available under the US Food and Drug Administration's emergency-use authorisation scheme.</li> <li>A point-of-care test that provides results within hours is available in some countries.[422] 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</li> </ul>	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

Test	Result
<p>as yet.[339] A pooled sensitivity of 64.8% and specificity of 98% has been reported with point-of-care tests.[423]</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Sensitivity and specificity of RT-PCR for diagnostic testing are unknown.[424]</li> <li>• 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] [338]</li> <li>• There is emerging evidence that saliva may be a reliable specimen for detecting SARS-CoV-2 by RT-PCR.[425] [426] A test that uses saliva has just been approved.[427]</li> <li>• The Food and Drug Administration has approved the first diagnostic test in the US with a home collection option, which allows for testing of a sample taken from the nose using a self-collection kit. After the sample is taken, it is sent in an insulated package to a designated laboratory for testing.[428]</li> </ul>	
<p><b>chest x-ray</b></p> <ul style="list-style-type: none"> <li>• Order in all patients with suspected pneumonia.</li> <li>• Unilateral lung infiltrates are found in 25% of patients, and bilateral lung infiltrates are found in 75% of patients.[28] [29] [344]</li> <li>• 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.[345]</li> </ul>	<p><b>unilateral or bilateral lung infiltrates</b></p>



## Other tests to consider

Test	Result
<p><b>computed tomography (CT) chest</b></p> <ul style="list-style-type: none"> <li>Consider a CT scan of the chest. Consult local guidance on whether to perform a CT scan. The British Society of Thoracic Imaging (BSTI) recommends CT imaging in patients with clinically suspected COVID-19 who are seriously ill if chest x-ray is uncertain or normal. <a href="#">[BSTI: radiology decision tool for suspected COVID-19]</a> Some institutions in the UK recommend a more pragmatic approach for patients with high clinical suspicion of COVID-19, with chest CT recommended only after two indeterminate or normal chest x-rays in combination with a negative RT-PCR test.<a href="#">[347]</a> 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.<a href="#">[348]</a></li> <li>Abnormal chest CT findings have been reported in up to 97% of hospitalised patients.<a href="#">[349]</a> Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.<a href="#">[350]</a> CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients.<a href="#">[79]</a> <a href="#">[351]</a> Some patients may present with a normal chest finding despite a positive RT-PCR.<a href="#">[352]</a> 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.<a href="#">[353]</a></li> <li>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.<a href="#">[354]</a></li> <li>Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity and, less frequently, areas of consolidation. Abnormalities are more common in the lower lobes and are predominantly unilateral. Pleural effusion is rare.<a href="#">[356]</a></li> <li>CT scan generally shows an increase in the size, number, and density of ground-glass opacities in the early follow-up period, with a progression to mixed areas of ground-glass opacities, consolidations, and crazy paving peaking at day 10 to 11, before gradually resolving or persisting as patchy fibrosis.<a href="#">[354]</a></li> <li>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.<a href="#">[421]</a> A sensitivity of 96% has been reported in another meta-analysis.<a href="#">[429]</a></li> <li>In a cohort of over 1000 patients in a hyperendemic area in China, chest CT had a higher sensitivity for diagnosis of COVID-19</li> </ul>	<p><b>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</b></p>

Test	Result
<p>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.<a href="#">[430]</a></p> <p><a href="#">[Fig-2]</a></p>	
<p><b>serology</b></p> <ul style="list-style-type: none"> <li>• Serological testing is becoming increasingly available for use; however, while rapid antibody detection kits have been approved in Europe and the US 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.<a href="#">[339]</a></li> <li>• 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, IgM and IgG, or total antibody. The test's positive predictive value should be high (99.5% or greater), and 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. Serological tests should not be used to make decisions about people returning to their workplace.<a href="#">[340]</a></li> <li>• Antibody responses to SARS-CoV-2 typically occur during the first 1 to 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.<a href="#">[341]</a> <a href="#">[342]</a> Serum samples can be stored to retrospectively define cases when validated serology tests become available.</li> </ul>	<p><b>positive for SARS-CoV-2 virus antibodies</b></p>

## Emerging tests

Test	Result
<b>antigen test</b> <ul style="list-style-type: none"> <li>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.<a href="#">[360]</a></li> </ul>	<b>positive for SARS-CoV-2 virus antigen</b>
<b>reverse transcription loop-mediated isothermal amplification (RT-LAMP)</b> <ul style="list-style-type: none"> <li>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.<a href="#">[357]</a> <a href="#">[358]</a> <a href="#">[359]</a></li> </ul>	<b>positive for SARS-CoV-2 viral RNA</b>
<b>lung ultrasound</b> <ul style="list-style-type: none"> <li>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.<a href="#">[345]</a></li> <li>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.</li> <li>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.<a href="#">[361]</a></li> <li>May be used in pregnant women and children.<a href="#">[362]</a> <a href="#">[363]</a></li> <li><a href="#">[BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas]</a></li> </ul>	<b>B-lines; pleural line abnormalities</b>

## Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
<b>Community-acquired pneumonia</b>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.<a href="#">[431]</a> <a href="#">[432]</a></li> </ul>	<ul style="list-style-type: none"> <li>• Blood or sputum culture or molecular testing: positive for causative organism.</li> <li>• RT-PCR: negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA (co-infections are possible).</li> <li>• CT chest: centrilobular nodules, mucoid impactions.<a href="#">[433]</a></li> </ul>
<b>Influenza infection</b>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.</li> <li>• 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.<a href="#">[434]</a></li> </ul>	<ul style="list-style-type: none"> <li>• RT-PCR: positive for influenza A or B viral RNA; negative for SARS-CoV-2 viral RNA (co-infections are possible).</li> <li>• 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.<a href="#">[435]</a> <a href="#">[436]</a></li> <li>• 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.<a href="#">[437]</a></li> </ul>

Condition	Differentiating signs / symptoms	Differentiating tests
<b>Common cold</b>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.</li> </ul>	<ul style="list-style-type: none"> <li>• RT-PCR: positive for causative organism; negative for SARS-CoV-2 viral RNA (co-infections are possible).</li> </ul>
<b>Other viral or bacterial respiratory infections</b>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.</li> <li>• Adenovirus and <i>Mycoplasma</i> should be considered in clusters of pneumonia patients, especially in closed settings such as military camps and schools.</li> </ul>	<ul style="list-style-type: none"> <li>• Blood or sputum culture of molecular testing: positive for causative organism.</li> <li>• RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).</li> </ul>
<b>Aspiration pneumonia</b>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Differentiating COVID-19 from aspiration pneumonia is not usually possible from signs and symptoms.</li> </ul>	<ul style="list-style-type: none"> <li>• RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).</li> <li>• CT chest: difficult to distinguish on CT; however, anterior lung involvement may be more suggestive of COVID-19 pneumonia.[438]</li> </ul>
<b>Pneumocystis jirovecii pneumonia</b>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Differentiating COVID-19 from pneumocystis jirovecii pneumonia is not usually</li> </ul>	<ul style="list-style-type: none"> <li>• Sputum culture: positive for <i>Pneumocystis</i>.</li> <li>• RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).</li> <li>• CT chest: ground-glass opacity is usually more diffusely distributed with a tendency to spare the subpleural regions.[433]</li> </ul>

Condition	Differentiating signs / symptoms	Differentiating tests
	<p>possible from signs and symptoms.</p> <ul style="list-style-type: none"> <li>Patients are usually immunocompromised (e.g., HIV positive) and duration of symptoms may be longer.</li> </ul>	
<b>Middle East respiratory syndrome (MERS)</b>	<ul style="list-style-type: none"> <li>Travel history to the Middle East or contact with a confirmed case of MERS.</li> <li>Differentiating COVID-19 from MERS is not possible from signs and symptoms.</li> <li>Initial data suggest that the clinical course of COVID-19 is less severe and the case fatality rate is lower compared with MERS.</li> </ul>	<ul style="list-style-type: none"> <li>Reverse-transcriptase polymerase chain reaction (RT-PCR): positive for MERS-CoV viral RNA.</li> </ul>
<b>Severe acute respiratory syndrome (SARS)</b>	<ul style="list-style-type: none"> <li>There have been no cases of SARS reported since 2004.</li> </ul>	<ul style="list-style-type: none"> <li>RT-PCR: positive for severe acute respiratory syndrome coronavirus (SARS-CoV) viral RNA.</li> </ul>
<b>Avian influenza A (H7N9) virus infection</b>	<ul style="list-style-type: none"> <li>May be difficult to differentiate based on epidemiological history as avian influenza H7N9 is endemic in China.</li> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>RT-PCR: positive for H7-specific viral RNA.</li> </ul>
<b>Avian influenza A (H5N1) virus infection</b>	<ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>RT-PCR: positive for H5N1 viral RNA.</li> </ul>
<b>Pulmonary tuberculosis</b>	<ul style="list-style-type: none"> <li>Consider diagnosis in endemic areas, especially in patients who are immunocompromised.</li> <li>History of symptoms is usually longer.</li> </ul>	<ul style="list-style-type: none"> <li>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</li> </ul>



Condition	Differentiating signs / symptoms	Differentiating tests
	<ul style="list-style-type: none"> <li>• Presence of night sweats and weight loss may help to differentiate.</li> </ul>	<ul style="list-style-type: none"> <li>• lymphadenopathy, and/or pleural effusion.</li> <li>• Sputum acid-fast bacilli smear and sputum culture: positive.</li> <li>• Molecular testing: positive for <i>Mycoplasma tuberculosis</i>.</li> </ul>
<b>Febrile neutropenia</b>	<ul style="list-style-type: none"> <li>• 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.[439]</li> <li>• Symptoms of COVID-19 and neutropenic sepsis may be difficult to differentiate at initial presentation.</li> </ul>	<ul style="list-style-type: none"> <li>• CBC: neutropenia.</li> <li>• RT-PCR: negative for SARS-CoV-2 viral RNA.</li> </ul>

## Diagnostic criteria

### World Health Organization: case definitions[139]

#### Suspect case

- A. Patients with acute respiratory illness (i.e., fever and at least one sign/symptom of respiratory disease such as cough or shortness of breath) AND a history of travel to or residence in a location reporting community transmission of COVID-19 during the 14 days prior to symptom onset; OR
- B. Patients with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; OR
- C. Patients with severe acute respiratory illness (i.e., fever and at least one sign/symptom of respiratory disease such as cough or shortness of breath) AND requiring hospitalisation AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

#### Probable case

- A. Suspect case for whom testing for the COVID-19 virus is inconclusive (inconclusive being the result of the test reported by the laboratory); OR
- B. Suspect case for whom testing could not be performed for any reason.

#### Confirmed case

- Patients with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

#### Definition of contact

- A contact is a person who 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 more than 15 minutes
  - Direct physical contact with a probable or confirmed case
  - Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment
  - Other situations as indicated by local risk assessments.
- Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken that led to confirmation.

[WHO: global surveillance for COVID-19 caused by human infection with COVID-19 virus]

# 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.

## 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.<sup>[2]</sup>

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

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

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).<sup>[444]</sup> Children are less likely to require hospitalisation, but if admitted, generally only require supportive care.<sup>[10] [17]</sup> The median time from onset of symptoms to hospital admission is around 7 days.<sup>[28] [367]</sup>

Overall, 19% of hospitalised patients require non-invasive ventilation, 17% require intensive care, 9% require invasive ventilation, and 2% require extracorporeal membrane oxygenation.<sup>[364]</sup> The most common reasons for intensive care unit admission are hypoxaemic respiratory failure leading to mechanical ventilation and hypotension.<sup>[445]</sup> 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).<sup>[446]</sup> 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.<sup>[444]</sup>

## 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.<sup>[2]</sup>

### 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.<sup>[2] [3]</sup> This decision requires careful clinical judgement and should be informed by an assessment of the patient's home environment.<sup>[440]</sup>

- 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 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.[447] Guidance on when to stop isolation depends on local circumstances and may differ between countries.

#### Infection prevention and control

- For patients in home isolation, advise patients and household members to follow appropriate infection prevention and control measures:
  - [\[WHO: home care for patients with COVID-19 presenting with mild symptoms and management of their contacts\]](#)
  - [\[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] [448] 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] [449] [450] [451] [452] [453] [454] [455] 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.[449]
- 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.[456]

#### 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] [449]
- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[2]

#### Monitor

- Closely monitor patients with risk factors for severe illness, and counsel patients about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain).[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.<sup>[2]</sup> <sup>[3]</sup>
- 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.<sup>[2]</sup> The Centers for Disease Control and Prevention 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.<sup>[447]</sup> <sup>[457]</sup> Guidance on when to stop isolation depends on local circumstances and may differ between countries.

## 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.<sup>[2]</sup> <sup>[3]</sup> 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.<sup>[2]</sup>

## Monitor

- Closely monitor patients for signs or symptoms of disease progression.
- If the patient is being managed at home, counsel them about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain). There is no evidence to support the use of pulse oximeters in the home setting.<sup>[2]</sup>
- 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.<sup>[2]</sup>

**Management of severe COVID-19#**

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

- 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<sub>2</sub> <90% on room air
- Severe disease in children is defined as having clinical signs of pneumonia plus at least one of the following:

- Central cyanosis or  $\text{SpO}_2 < 90\%$
- Severe respiratory distress
- General danger 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]
- 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  $\geq 5$ ), 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.[458]
- 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 Centers for Disease Control and Prevention 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.[457] Guidance on when to stop isolation depends on local circumstances and may differ between countries.

#### 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  $\text{SpO}_2 < 90\%$ .[2] [3] There is no evidence of benefit for oxygen therapy in patients with COVID-19 in the absence of hypoxaemia.[459]
- Target  $\text{SpO}_2$  to  $\geq 94\%$  during resuscitation in adults and children with emergency signs who require emergency airway management and oxygen therapy. Once the patient is stable, a target  $\text{SpO}_2 > 90\%$  in children and non-pregnant adults, and  $\geq 92\%$  to  $95\%$  in pregnant women, is recommended. Nasal prongs or a nasal cannula are preferred in young children.[2] Some guidelines recommend that  $\text{SpO}_2$  should be maintained no higher than  $96\%$ .[448]
- Some centres may recommend different  $\text{SpO}_2$  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.[460]
- 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.[461] 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.[462] [463] [464] [465] [466]

- 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 oxygenation.[2] Correct any electrolyte or metabolic abnormalities, such as hyperglycaemia or metabolic acidosis, according to local protocols.[467]
- Fever and pain: paracetamol or ibuprofen are recommended.[2] [448] 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] [449] [450] [451] [452] [453] [454] [455] 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.[449]
- 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.[449]
- 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] [449] 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.[449] 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.[468]
- 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] [469] [470]
- 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] [470] [471]

- The optimal dose is unknown. Standard prophylaxis doses are recommended over intermediate- or full treatment-dose regimens.[470] 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.[472] 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.[469]
- 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] [469] [470]
- 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.[469]

### 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] [418]
- 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.[419] 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.[418] 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.[418]
- 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 (preliminary results from a preprint study, not peer reviewed) 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.[473]
- 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.[474]
- 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. Assess whether the patient is suitable for corticosteroid therapy before starting therapy. The safety of coadministering dexamethasone and remdesivir is not known.[3]

#### Experimental therapies

- Administer experimental therapies such as remdesivir, hydroxychloroquine, lopinavir/ritonavir, and plasma therapy only in the context of a clinical trial.[2] See 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

- 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.[449]
- 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 Centers for Disease Control and Prevention 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.[457] Guidance on when to stop isolation depends on local circumstances and may differ between countries.

#### 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.[475] [476] [477] [478]
- 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.[479] NHS England recommends CPAP as the preferred form of non-invasive ventilation. 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.[480] Other guidelines recommend HFNO over non-invasive ventilation, unless HFNO is not available.[3] [448] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[481]
- Early CPAP may provide a bridge to invasive mechanical ventilation. Reserve the use of BiPAP for patients with hypercapnic acute or chronic ventilatory failure.[480]
- 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.[482]
- Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions, they require urgent endotracheal intubation.[2] [448]

- 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.[\[483\]](#) 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.[\[146\]](#) Patients spent an average of 18 days on a ventilator (range 9-28 days).[\[152\]](#)
- 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<sub>2</sub> 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.[\[2\]](#) [\[3\]](#) [\[448\]](#) NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[\[484\]](#)
- 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.[\[485\]](#) [\[486\]](#) [\[487\]](#) [\[488\]](#) [\[489\]](#) [\[490\]](#) However, this approach has been criticised.[\[491\]](#) [\[492\]](#) 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.[\[493\]](#) 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.[\[485\]](#) PEEP should always be carefully titrated.[\[461\]](#)
- 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.[\[2\]](#) [\[3\]](#) [\[448\]](#) Longer durations may be feasible in some patients.[\[494\]](#) 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.[\[495\]](#) 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.[\[496\]](#) [\[497\]](#)
- Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[\[3\]](#) [\[448\]](#)
- 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] [448]

#### Extracorporeal membrane oxygenation

- Consider extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[2] [448] [498] [499] ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[500]
- 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 is not promising, although it may play a useful role in salvaging select patients.[501] [502]

#### 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 (see above).
- 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.[470]

#### Corticosteroids

- Consider low-dose dexamethasone for the management of hospitalised patients with COVID-19 who require oxygen or ventilation (see above).
- In relation to high-dose corticosteroids, 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.[448] Other guidelines do not routinely recommend systemic corticosteroids for the treatment of COVID-19 unless they are indicated for another reason (e.g., exacerbation of asthma or chronic obstructive pulmonary disease, septic shock, ARDS) and then only after a risk/benefit analysis, or used in the context of a clinical trial.[2] [503] A meta-analysis of over 13,000 patients found that systemic high-dose corticosteroid treatment in adults with COVID-19 did not reduce mortality risk, duration of lung inflammation, or length of hospital stay, and long-term use was associated with an increased risk of adverse effects.[504]

#### 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.

There has been some suggestion that lung injury due to COVID-19 may be similar to high-altitude pulmonary oedema (HAPO); however, there is no evidence to support this, and treatments used for HAPO (e.g., acetazolamide) should not be used for the treatment of COVID-19.[394]

## 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]

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]

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.[505] Another study in a New York obstetric population found that 88% of women who tested positive for SARS-CoV-2 at admission were asymptomatic at presentation.[506] The prevalence of asymptomatic SARS-CoV-2-positive pregnant women was lower (<3%) in a population in Connecticut.[507] 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.[202]

### 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.[343] [508] [509]
- 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.[343] [509] [510] 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.[511]

## 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] [343] [509] Avoid using birthing pools in patients with suspected or confirmed infection.[511]
- Delayed umbilical cord clamping (not earlier than 1 minute after birth) is recommended for improved maternal and infant health and nutrition outcomes. The risk of transmission via blood is thought to be minimal, and there is no evidence that delayed cord clamping increases the risk of viral transmission from the mother to the newborn.[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.[512]

## Newborn care

- Experts are divided on separating mother and baby after delivery; make decisions on a case-by-case 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.[513]
- The Centers for Disease Control and Prevention recommends that temporary separation of a newborn from a mother with confirmed or suspected COVID-19 should be strongly considered. However, the risks and benefits should be discussed with the mother and decisions made in accordance with the mother's wishes. If separation is not undertaken, measures to minimise the risk of transmission should be implemented.[514] 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.[515]
- 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.<sup>[511]</sup>

- 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  $\geq 24$  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.<sup>[512]</sup>

## 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](#)

<b>Acute ( summary )</b>		
<b>mild COVID-19</b>		
	<b>1st</b>	<b>consider home isolation</b>
	<b>plus</b>	<b>monitoring</b>
	<b>plus</b>	<b>symptom management and supportive care</b>
	<b>adjunct</b>	<b>antipyretic/analgesic</b>
<b>moderate COVID-19</b>		
	<b>1st</b>	<b>consider home isolation or hospital admission</b>
	<b>plus</b>	<b>monitoring</b>
	<b>plus</b>	<b>symptom management and supportive care</b>
	<b>adjunct</b>	<b>antibiotics</b>
	<b>adjunct</b>	<b>antipyretic/analgesic</b>
<b>severe COVID-19</b>		
	<b>1st</b>	<b>hospital admission</b>
	<b>plus</b>	<b>consider oxygen therapy</b>
	<b>plus</b>	<b>symptom management and supportive care</b>
	<b>plus</b>	<b>venous thromboembolism prophylaxis</b>
	<b>plus</b>	<b>monitoring</b>
	<b>plus</b>	<b>consider antibiotics</b>
	<b>adjunct</b>	<b>dexamethasone</b>
	<b>adjunct</b>	<b>treatment of co-infections</b>
	<b>adjunct</b>	<b>antipyretic/analgesic</b>
	<b>adjunct</b>	<b>experimental therapies</b>
	<b>adjunct</b>	<b>discharge and rehabilitation</b>
<b>critical COVID-19</b>		
	<b>1st</b>	<b>intensive/critical care unit admission</b>
	<b>plus</b>	<b>consider high-flow nasal oxygen or non-invasive ventilation</b>
	<b>plus</b>	<b>consider invasive mechanical ventilation</b>
	<b>adjunct</b>	<b>inhaled pulmonary vasodilator</b>
	<b>adjunct</b>	<b>extracorporeal membrane oxygenation</b>

<b>Acute</b>		<b>( summary )</b>
	<b>adjunct</b>	<b>management of sepsis/septic shock</b>
	<b>adjunct</b>	<b>symptom management and supportive care</b>
	<b>adjunct</b>	<b>dexamethasone</b>
	<b>adjunct</b>	<b>experimental therapies</b>
	<b>adjunct</b>	<b>discharge and rehabilitation</b>
	<b>adjunct</b>	<b>palliative care</b>

## Treatment options

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



## Acute

## mild COVID-19

## 1st

## consider home isolation

» 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.[440] 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 COVID-19 presenting with mild symptoms 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 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.[447] Guidance on when to stop isolation depends on local circumstances and may differ between countries.

## plus

## monitoring

## Acute

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.[449]

» 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).[449]

» 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.[456]

**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] [448] There is no evidence at

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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] [449] [450] [451] [452] [453] [454] [455]

» 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]

» 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 COVID-19 presenting with mild symptoms 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] [457] The US Centers for Disease Control and Prevention 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.[447] [457] Guidance on when to stop

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- isolation depends on local circumstances and may differ between countries.
- 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 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.[449]
  - » 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).[449]
  - » 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.[456]
- 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.

## Acute

## adjunct

The regimen should be based on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.[2]

**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] [448] 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] [449] [450] [451] [452] [453] [454] [455]

» 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<sub>2</sub> <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<sub>2</sub> <90%, severe respiratory distress, general danger

## Acute

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. [Clinical frailty scale] Involve critical care teams in discussions about admission to critical care.[458]

» 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]

» 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 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.[457] Guidance on when to stop isolation depends on local circumstances and may differ between countries.

**plus consider oxygen therapy**

Treatment recommended for ALL patients in selected patient group

» Start supplemental oxygen therapy immediately in any patient with emergency signs (i.e., obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions), or any patient without emergency signs and SpO<sub>2</sub> <90%.[2] [3]

» Target SpO<sub>2</sub> 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<sub>2</sub> >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<sub>2</sub> should be maintained no higher than 96%.[448]



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» Some centres may recommend different SpO<sub>2</sub> 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.[460]

» 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.[461] 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.[462] [463] [464] [465] [466]

» 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.[467]

» 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.[449]

» 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

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moderate to severe breathlessness or patients who are distressed.[449]

» 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] [449] 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.[449] 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.[468]

» 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**

» **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

## Acute

not influence a paediatrician's recommendations about VTE prophylaxis in hospitalised children. Pregnant women should be managed by a specialist.[\[2\]](#) [\[3\]](#) [\[469\]](#) [\[470\]](#)

» 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.[\[2\]](#) [\[470\]](#) [\[471\]](#)

» The optimal dose is unknown. Standard prophylaxis doses are recommended over intermediate- or full treatment-dose regimens.[\[470\]](#) 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.[\[472\]](#) 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.[\[469\]](#)

» 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.[\[3\]](#) [\[469\]](#) [\[470\]](#)

» 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.[\[469\]](#)

**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**

## Acute

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] [418]

» 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.[419] 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.[418] 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.[418]

» 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]

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**adjunct dexamethasone**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **dexamethasone**: 6 mg orally/intravenously once daily 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 (preliminary results from a preprint study, not peer reviewed) 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.[473]

» 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.[474]

» 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. Assess whether the patient is suitable for corticosteroid therapy before starting therapy. The safety of coadministering dexamethasone and remdesivir is not known.[3]

**adjunct treatment of co-infections**

Treatment recommended for SOME patients in selected patient group

## Acute

## adjunct

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

**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] [448] 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] [449] [450] [451] [452] [453] [454] [455]

» 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

» Administer experimental therapies such as remdesivir, hydroxychloroquine, lopinavir/ritonavir, and plasma therapy only in the context of a clinical trial.[2] See Emerging section for more information.

## adjunct

**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



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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.[449]

» 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]

» 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 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.[457] Guidance on when to stop isolation depends on local circumstances and may differ between countries.

**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]

## Acute

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.[479] NHS England recommends CPAP as the preferred form of non-invasive ventilation. 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.[480] Other guidelines recommend HFNO over non-invasive ventilation, unless HFNO is not available.[3] [448] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[481]

» Early CPAP may provide a bridge to invasive mechanical ventilation. Reserve the use of BiPAP for patients with hypercapnic acute or chronic ventilatory failure.[480]

» Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions, they require urgent endotracheal intubation.[2] [448]

**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]

» Endotracheal intubation should be performed by an experienced provider using airborne

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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<sub>2</sub>) 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] [448] NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[484]

» 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.[485] [486] [487] [488] [489] [490] However, this approach has been criticised.[491] [492] 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.[493] 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.[485] PEEP should always be carefully titrated.[461]

» 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] [448] Longer durations may be feasible in some patients.[494]

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- » Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[\[3\]](#) [\[448\]](#)
- 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.[\[3\]](#) [\[448\]](#)
- 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.[\[2\]](#) [\[448\]](#) [\[498\]](#) [\[499\]](#) ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[\[500\]](#)
- » 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 is not promising, although it may play a useful role in salvaging select patients.[\[501\]](#) [\[502\]](#)
- 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 symptom management and supportive care**
- Treatment recommended for SOME patients in selected patient group
- » Consider fluid and electrolyte management, antimicrobial treatment, and experimental therapies as appropriate. See Severe COVID-19 section above for more detailed information.
- » Manage symptoms such as fever, pain, cough, breathlessness, anxiety, agitation, delirium, depression, or insomnia as appropriate. See Severe COVID-19 section above for more detailed information.
- » Venous thromboembolism prophylaxis is recommended in critically ill patients. Low molecular weight heparin is the preferred

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option, with unfractionated heparin considered a suitable alternative and preferred over fondaparinux.<sup>[470]</sup> See Severe COVID-19 section above for more detailed information.

» Implement standard interventions to prevent complications associated with critical illness.<sup>[2]</sup>

**adjunct dexamethasone**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **dexamethasone**: 6 mg orally/intravenously once daily 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 (preliminary results from a preprint study, not peer reviewed) 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.<sup>[473]</sup>

» 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.<sup>[474]</sup>

» 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. Assess whether the patient is suitable for corticosteroid therapy before starting therapy.

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- The safety of coadministering dexamethasone and remdesivir is not known.<sup>[3]</sup>
- adjunct experimental therapies**
- Treatment recommended for SOME patients in selected patient group
- » Administer experimental therapies such as remdesivir, hydroxychloroquine, lopinavir/ritonavir, and plasma therapy only in the context of a clinical trial.<sup>[2]</sup> See Emerging section for more information.
- adjunct 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.<sup>[2]</sup>
- 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.<sup>[2]</sup> Follow local palliative care guidelines.



# 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.[\[516\]](#) [\[517\]](#) [\[WHO: off-label use of medicines for COVID-19\]](#) 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.[\[518\]](#) 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).[\[519\]](#) 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; tocilizumab; and convalescent plasma. [\[RECOVERY trial\]](#)

## Remdesivir

A novel, investigational, 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).[\[520\]](#) 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.[\[521\]](#) The National Institutes of Health guidelines recommend remdesivir for the treatment of COVID-19 in hospitalised patients with severe disease, defined as  $\text{SpO}_2 \leq 94\%$  on ambient air (at sea level), requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation. The guidelines panel recommends that patients who are not intubated should receive 5 days of treatment; however, it acknowledges that some experts may extend the treatment course to 10 days in those who are mechanically ventilated or on extracorporeal membrane oxygenation, or those who do not respond adequately after 5 days. The guidelines panel does not recommend for or against remdesivir for the treatment of mild or moderate COVID-19 as there are insufficient data.[\[3\]](#) A 5-day course was found to be as safe and efficacious as a 10-day course in patients with severe disease not requiring ventilation; however, this was not a placebo-controlled trial.[\[522\]](#) Preliminary results from an open-label phase 3 trial in patients with moderate disease found that a 5-day course resulted in greater clinical improvement at day 11 compared with standard of care; however, full results are yet to be published.[\[523\]](#) Early results from one trial of patients treated with remdesivir on a compassionate-use basis indicated that approximately two-thirds of patients showed signs of clinical improvement (68% of patients had an improvement in oxygen support requirements); however, the study had no control arm and the majority of patients reported adverse

effects.[524] A randomised, placebo-controlled trial in 240 hospitalised patients with severe COVID-19 in China found that remdesivir was not associated with significantly clinical benefits; however, the trial was underpowered, and while it showed some non-significant trends for benefit, it did not meet its primary end point.[525] A 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.[526] Remdesivir appears to be safe to use in pregnancy.[527] 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.[528] 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.[529] The UK Medicines and Healthcare products Regulatory Agency has issued a positive opinion for the use of remdesivir as part of its COVID-19 Early Access to Medicines Scheme.[530] A trial of inhaled remdesivir is about to start phase 1 clinical trials.

## Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine 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.[531] [532] They are being trialled in patients for the treatment and prophylaxis of COVID-19. Initial data seemed promising, but evidence so far is weak and conflicting.[533] 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.[534] However, this trial has been criticised for its limitations, and results from a similar trial could not replicate these findings.[535] [536] 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.[537] Early results from the largest randomised controlled trial completed so far 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).[538] 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.[539] 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.[540] 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.[541] 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.[542] [543] 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.[544] As a consequence of this, the WHO stopped the hydroxychloroquine arm of the Solidarity trial on 17 June.[545] 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.[546] Hydroxychloroquine has similar therapeutic effects to chloroquine, but fewer adverse effects, is considered safe in pregnancy, and is more readily available in some countries.[547] Both drugs must be

used with caution in patients with pre-existing cardiovascular disease due to the risk of arrhythmias.[548] It is reasonable to do a baseline echocardiogram before treatment whenever possible, particularly in patients who are critically ill.[549] 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.[550] Because chloroquine/hydroxychloroquine and azithromycin can both cause QT interval prolongation, caution is recommended when using these drugs together.[551] [552] 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%).[553] 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.[554] This combination is not recommended except in the context of a clinical trial.[3] Caution is recommended with the dosing regimen used for chloroquine due to the risk of chloroquine poisoning.[555] Guidelines in China and Italy recommend these drugs for the treatment of COVID-19; however, this is based on weak evidence.[556] 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.[448] 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 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.[498] 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.[557] 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.[558] 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.[559] 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.[560] There is currently no strong evidence of efficacy of hydroxychloroquine or chloroquine in the treatment or prevention of COVID-19.[561] [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.[562] 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.[563] There is currently no strong evidence of efficacy of lopinavir/ritonavir in the treatment of COVID-19. Lopinavir/ritonavir (and other protease inhibitors) 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] Lopinavir/ritonavir is considered safe in pregnancy.[527]

## Convalescent plasma

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.[564] 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.[565] 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.[566] In the US, the FDA is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of single patient emergency investigational new drug applications, and has issued guidance for its use. The FDA is encouraging patients who have recovered (complete resolution of symptoms for at least 2 weeks prior to donation; a negative

reverse-transcription polymerase chain reaction [RT-PCR] test is not necessary to qualify for donation) to donate their plasma.[567] [568] [569] There is currently insufficient evidence to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.[3] The authors of a Cochrane rapid review were uncertain as to whether convalescent plasma is an effective treatment for 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.[570]

## Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is being trialled in some patients with COVID-19.[29] [571] 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.[572] There is currently insufficient evidence to recommend IVIG for the treatment of COVID-19.[573] 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.[574] 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.[575] [576] Novel multi-antibody cocktail therapies are also in development for prophylaxis or treatment.[577]

## Treatments for cytokine release syndrome

Interleukin-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.[578] [579] [580] [581] [582] [583] [584] [585] Tocilizumab and sarilumab are already approved in some countries for the treatment of rheumatological conditions, siltuximab is approved in some countries for Castleman's disease, and tocilizumab is approved in some countries for the treatment of chimeric antigen receptor (CAR) T-cell-induced severe or life-threatening cytokine release syndrome. However, the decision to suppress the immune system of a critically unwell patient with COVID-19 is a difficult one; the beneficial anti-inflammatory effects of anti-inflammatory drugs must be weighed against the possibly detrimental effects of impairment of immunity.[586] A retrospective cohort study found that clinical improvement and 28-day mortality were not statistically different between tocilizumab and standard of care.[587] Other studies found that the use of tocilizumab was associated with significantly shorter duration of vasopressor support, and that it may reduce the risk of non-invasive mechanical ventilation or death in patients with severe disease.[588] [589] Other drugs currently in clinical trials for the treatment of COVID-19-associated cytokine release syndrome include anakinra (an interleukin-1 inhibitor); the Janus kinase inhibitors fedratinib, ruxolitinib, and baricitinib; and the C-C chemokine receptor type 5 (CCR5) antagonist leronlimab.[590] [591] [592] [593] [594] 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.[595] A small prospective cohort study found that anakinra significantly reduced the need for invasive mechanical ventilation and mortality in patients with severe disease.[596] There is currently insufficient evidence to recommend either for or against the use of interleukin-6 inhibitors or anakinra for the treatment of COVID-19. Janus kinase inhibitors should only be used in the context of a clinical trial.[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.[597] 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.[598]



## 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.<sup>[599]</sup>

## 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.<sup>[600]</sup> 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.<sup>[601]</sup>

## 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 is the first candidate to be selected as part of the UK's Accelerating COVID-19 Research and Development (ACCORD) study. The multicentre, phase 2, adaptive randomisation platform trial aims to assess the safety and efficacy of multiple candidates.<sup>[602]</sup>

## 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 virus.<sup>[603]</sup> <sup>[604]</sup> <sup>[605]</sup> However, some experts believe that these drugs may worsen COVID-19 due to overexpression of ACE2 in people taking these drugs.

## Other antivirals

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).<sup>[606]</sup> <sup>[607]</sup> <sup>[608]</sup> <sup>[609]</sup> <sup>[610]</sup> <sup>[611]</sup> <sup>[612]</sup> <sup>[613]</sup> <sup>[614]</sup> Umifenovir monotherapy may be superior to lopinavir/ritonavir in treating COVID-19 in terms of reduced viral load and shorter duration of positive molecular tests.<sup>[615]</sup> 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.<sup>[616]</sup>

## Vitamin C

Vitamin C supplementation has shown promise in the treatment of viral infections.<sup>[617]</sup> High-dose intravenous vitamin C is being trialled in some centres for the treatment of severe COVID-19.<sup>[618]</sup>

## Vitamin D

Vitamin D supplementation has been associated with a reduced risk of respiratory infections such as influenza in some studies.<sup>[619]</sup> <sup>[620]</sup> <sup>[621]</sup> A small retrospective observational preprint study (not peer reviewed) suggests a link between vitamin D insufficiency and COVID-19 severity.<sup>[622]</sup> However, further research is needed.<sup>[623]</sup> <sup>[624]</sup> <sup>[625]</sup> <sup>[626]</sup> Vitamin D is being trialled in patients with COVID-19.<sup>[627]</sup> <sup>[628]</sup> However, there is no evidence to recommend vitamin D for the prophylaxis or treatment of COVID-19 as yet.<sup>[629]</sup> Public Health England recommends that people consider taking a vitamin D supplement for bone and muscle health due to a lack of sun exposure as a result of lockdown measures.<sup>[630]</sup>

## 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.<sup>[631]</sup>

## Hyperbaric oxygen

Preliminary evidence suggests that hyperbaric oxygen treatment has been successfully used to treat deteriorating, severely hypoxaemic patients with severe COVID-19.<sup>[632]</sup> <sup>[633]</sup> Clinical trials are currently recruiting.<sup>[634]</sup> <sup>[635]</sup>

## Nitric oxide

Studies indicate that nitric oxide may help to reduce respiratory tract infection by inactivating viruses and inhibiting their replication in epithelial cells.<sup>[636]</sup> 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 awarded fast-track designation by the FDA for the treatment of acute lung injury/acute respiratory distress syndrome associated with COVID-19. Intravenous and inhaled formulations are currently in phase 2 and 3 clinical trials in the US.<sup>[637]</sup> <sup>[638]</sup>



# Recommendations

## Monitoring

Regularly monitor the following in hospitalised patients to facilitate early recognition of deterioration and monitor for complications:[2] [788]

- 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.[816]

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.[509] Perform fetal growth ultrasound 14 days after resolution of symptoms.[511]

## 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).[274] [275]
- [BMJ Learning: Covid-19 – handwashing technique and PPE videos]
- [WHO: coronavirus disease (COVID-19) advice for the public]

Face masks

- 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).[83]
- 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.[280]
- [\[WHO: coronavirus disease \(COVID-19\) advice for the public – when and how to use masks\]](#)
- [\[Public Health England: how to wear and make a cloth face covering\]](#)
- [\[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: coronavirus \(COVID-19\)\]](#)
  - [\[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.[817]
- 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).[818] [819] [820] [821] Transmission between cats has also been reported.[822]
- 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.[823]
- [\[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

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.<sup>[824]</sup>

#### Resources

- [\[WHO: coronavirus disease \(COVID-19\) pandemic\]](#)
- [\[CDC: coronavirus \(COVID-19\)\]](#)
- [\[NHS UK: coronavirus \(COVID-19\)\]](#)

# Complications

Complications	Timeframe	Likelihood
<b>comorbidities</b>	<b>short term</b>	<b>high</b>
<p>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.</p>		
<b>venous thromboembolism</b>	<b>short term</b>	<b>high</b>
<p>Coagulopathy in COVID-19 has a prothrombotic character, which may explain reports of thromboembolic complications.<sup>[696]</sup> 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).<sup>[472]</sup></p> <p>Venous thromboembolism (pulmonary embolism or deep vein thrombosis) has been reported in 20% to 31% of patients with severe COVID-19 in the intensive care unit (including some patients who were on thromboprophylaxis), and may be associated with poor prognosis.<sup>[697] [698] [699] [700] [701] [702] [703]</sup> Other studies have reported higher rates of 46% to 85%.<sup>[704] [705] [706]</sup></p> <p>Patients with very high D-dimer levels have the greatest risk of thrombosis and may benefit from active monitoring.<sup>[410] [411]</sup> If venous thromboembolism is suspected, perform a computed tomographic angiography or ultrasound of the venous system of the lower extremities.<sup>[707]</sup></p> <p>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.<sup>[3]</sup></p> <p>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.<sup>[470]</sup></p> <p>A high incidence (14.7%) of asymptomatic deep vein thrombosis was reported in a cohort of patients with COVID-19 pneumonia.<sup>[708]</sup> An autopsy study of 12 patients revealed deep vein thrombosis in 58% of patients in whom venous thromboembolism was not suspected before death.<sup>[709]</sup> 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.</p> <p>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.<sup>[710]</sup></p>		

Complications	Timeframe	Likelihood
<p>Antiphospholipid antibodies and lupus anticoagulant have been detected in a small number of patients. The presence of these antibodies can rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis. 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.[711] [712] [713]</p> <p>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.[714] [715] [716]</p> <p>Cases of arterial thrombosis, cerebral venous thrombosis, and acute limb ischaemia secondary to thrombosis have been reported.[717] [718] [719] [720] [721]</p>		
cardiovascular complications	short term	medium
<p>COVID-19 is associated with a high inflammatory burden that can result in cardiovascular complications with a variety of clinical presentations. Inflammation in the vascular system can result in diffuse microangiopathy with thrombosis. Inflammation in the myocardium can result in myocarditis, heart failure, arrhythmias, acute coronary syndrome, rapid deterioration, and sudden death.[722] [723] [724] These complications can present on presentation or develop as the severity of illness worsens.[725] 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.[726]</p> <p>Acute myocardial injury (defined by elevated cardiac biomarkers) has been reported in 5% to 31% of patients, and is associated with severe outcomes and mortality in patients with COVID-19.[727]</p> <p>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.[725] [728] [729] [730] [731] The mortality of patients with cardiovascular disease was 22% in one retrospective study, compared with the mortality of the overall population in the study, which was 9.8%.[732] Patients with underlying cardiovascular disease but without myocardial injury have a relatively favourable prognosis.[733]</p> <p>Predictors for myocardial injury include older age, presence of cardiovascular-related comorbidities, and elevated C-reactive protein. Elevated myocardial markers predict risk for in-hospital mortality.[734]</p> <p>The most frequent cardiovascular complications in hospitalised patients are heart failure, myocardial injury, arrhythmias, and acute coronary syndrome.[735] Cases of fulminant myocarditis, cardiomyopathy, cardiac tamponade, myopericarditis with systolic dysfunction, pericarditis and pericardial effusion, ST-segment elevation (indicating potential acute myocardial infarction), cor pulmonale, and takotsubo syndrome have also been reported.[9] [659] [662] [736] [737] [738] [739] [740]</p> <p>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.[741]</p> <p>Monitor blood pressure, heart rate, and fluid balance, and perform continuous ECG monitoring in all patients with suspected or confirmed acute myocardial injury.[741]</p> <p>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</p>		

Complications	Timeframe	Likelihood
<p>specialists.[726] It is important to consider that drugs such as hydroxychloroquine and azithromycin may prolong the QT interval and lead to arrhythmias.[741]</p> <p>Guidelines for the management of COVID-19-related myocarditis are available.[742]</p> <p>Infection may have longer-term implications for overall cardiovascular health; however, further research is required.[743]</p>		
<b>acute kidney injury</b>	<b>short term</b>	<b>medium</b>
<p>The overall incidence of acute kidney injury in patients with COVID-19 is approximately 4% to 9%; incidence is higher in patients with severe or critical illness. The degree of acute kidney injury is closely associated with disease severity and prognosis. Patients have a poor prognosis, especially those who require renal replacement therapy.[744] [745]</p> <p>In retrospective studies in New York, 36.6% to 78% of hospitalised patients went on to develop acute kidney injury, and of these 14.3% to 35.2% required renal replacement therapy. Nearly 90% of patients on mechanical ventilation developed acute kidney injury, and 97% of patients requiring renal replacement therapy were on ventilators.[446] [746] Data from the UK indicate that approximately 31% of patients on ventilators (and 4% not on ventilators) require renal replacement therapy.[747] Similarly, 31% of critically ill patients in a New York study required dialysis.[152] 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.[748]</p> <p>Can develop at any time before or during hospital admission. Risk factors include age <math>\geq 65</math> years, Black ethnicity, history of acute kidney injury, chronic kidney disease, cardiovascular disease, hypertension, heart failure, hepatic disease, and diabetes.[746] [747] Causes include haemodynamic changes, hypovolaemia, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology, or rhabdomyolysis.[747] Direct kidney infection has been confirmed in an autopsy study of a single patient.[749]</p> <p>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.[747]</p> <p>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.[747]</p> <p>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.[747] 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]</p> <p>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.[747]</p> <p>Acute kidney injury is associated with poor prognosis.[746]</p> <p>Cases of nephritis and collapsing glomerulopathy have been reported.[750] [751]</p>		
<b>acute liver injury</b>	<b>short term</b>	<b>medium</b>



Complications	Timeframe	Likelihood
<p>Abnormal liver function, predominantly elevated aspartate aminotransferase, has been reported in up to half of patients with COVID-19. While it is common, it is not severe in most cases. Risk factors associated with severe liver injury include older age, pre-existing liver disease, and severe COVID-19.[752]</p> <p>Abnormal liver function is associated with a significant increase in the severity of COVID-19 infection.[753]</p> <p>Medications used in the treatment of COVID-19 (e.g., lopinavir/ritonavir) may have a detrimental effect on liver injury.[752]</p> <p>Guidelines on the management of liver derangement in patients with COVID-19 have been published.[754]</p>		
neurological complications	short term	medium
<p>Patients with severe illness commonly have neurological complications, possibly due to viral invasion of the central nervous system (SARS-CoV-2 has been detected in the brain and cerebrospinal fluid) or systemic illness.</p> <p>Neurological symptoms have been reported in 36% to 57% of patients in case series, and were more common in patients with severe illness.[755] [756] 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.[757]</p> <p>Complications include acute cerebrovascular disease, impairment of consciousness, ataxia, neuralgia, seizures, musculoskeletal injury, corticospinal tract signs, meningitis, encephalitis, encephalopathy, transverse myelitis, and Guillain-Barre syndrome. Patients may present with these signs/symptoms, or they may develop them during the course of the disease.[758] [759]</p> <p>Ischaemic stroke (confirmed on imaging) was reported in 0.9% of patients in a retrospective cohort study of hospitalised patients with COVID-19 in New York. Most strokes were cryptogenic.[760] Guidelines for the management of acute ischaemic stroke in patients with COVID-19 infection have been published.[761]</p>		
cytokine release syndrome	short term	low
<p>Cytokine release syndrome may cause ARDS or multiple-organ dysfunction, which may lead to death.[762] 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.[28] [379] [420] [763] Interleukin-6, in particular, has been associated with severe COVID-19 and increased mortality.[668]</p> <p>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.[764]</p> <p>Anti-inflammatory/immunosuppressive treatments (e.g., tocilizumab, hydroxychloroquine/chloroquine, Janus kinase inhibitors) are being trialled in COVID-19 patients.[765] See Emerging section for more information.</p> <p>Cytokine release syndrome has been reported in children, although cases appear to be rare.[766] See section below on paediatric multisystem inflammatory syndrome.</p>		
paediatric inflammatory multisystem syndrome	short term	low
<p>A rare, emerging inflammatory disease in children that has been temporally associated with COVID-19. It appears to be a post-infectious manifestation that can appear 4 to 5 weeks after infection (including in</p>		



Complications	Timeframe	Likelihood
<p>children who had initial asymptomatic or mild infection). It has been estimated that the risk is 2 per 10,000 children, based on French surveillance data.<a href="#">[767]</a> A small number of deaths have been reported.<a href="#">[768]</a></p> <p>The syndrome shares common features with Kawasaki disease, toxic shock syndrome, bacterial meningitis, and macrophage activation syndromes. Common features include abdominal pain, other gastrointestinal symptoms, and cardiac inflammation (elevated troponin and pro-B-type natriuretic peptide levels).<a href="#">[769]</a> <a href="#">[770]</a> <a href="#">[771]</a> <a href="#">[772]</a> However, patients can present with a wide spectrum of signs, symptoms, and disease severity ranging from fever and inflammation to myocardial injury, shock, and coronary artery aneurysms.<a href="#">[773]</a></p> <p>Gastrointestinal symptoms are prominent and were reported in 84% of children in one cohort (accompanied by fever in 100% of children and rash in 70.5%).<a href="#">[774]</a></p> <p>Abnormal cardiac findings are common; 60% of children in one cohort had non-specific ST/T-wave abnormalities, and about one third had moderate or severe ventricular dysfunction on electrocardiogram at admission.<a href="#">[775]</a></p> <p>A retrospective review at a centre in Bergamo province, Italy, reports a higher number of cases of Kawasaki-like disease during the COVID-19 epidemic, with a monthly incidence 30 times greater than the monthly incidence of the previous 5 years, and a clear starting point after the first case of COVID-19 was diagnosed. The clinical and biochemical features of these patients differ from the centre's historical cohort of patients with Kawasaki disease. The authors conclude that there is a strong association between this syndrome and the COVID-19 epidemic.<a href="#">[776]</a></p> <p>A retrospective study in France and Switzerland identified 35 children with fever and acute heart failure possibly associated with this syndrome. The median age at admission was 10 years, and comorbidities were present in 28% of children. Gastrointestinal symptoms were prominent. Inflammation markers were suggestive of cytokine release syndrome and macrophage activation. Left ventricular ejection fraction was &lt;30% in one third of patients. Some 88% of patients tested positive for SARS-CoV-2. All patients were treated with immunoglobulin, and some received corticosteroids. All patients recovered.<a href="#">[777]</a></p> <p>Another retrospective study in France identified 21 children with features of Kawasaki disease. Of these children, 57% had African ancestry. The median time from earlier onset of viral symptoms to the onset of Kawasaki-like illness was 45 days; 57% presented with Kawasaki disease shock syndrome and 76% presented with myocarditis. Approximately 90% of patients had positive molecular or serological tests for SARS-CoV-2. All patients had gastrointestinal symptoms early in the course of illness and elevated inflammatory markers. All patients were treated successfully and discharged.<a href="#">[778]</a></p> <p>A retrospective study in New York found that the median age of children was 10 years; 61% were male, 45% were Hispanic/Latino, and 39% were Black. Comorbidities were present in 45% of children. Fever and vomiting were the most common presenting symptoms, and depressed left ventricular ejection fraction was found in 63% of children. Inflammatory markers were elevated in all patients. All but one patient survived.<a href="#">[779]</a></p> <p>The Royal College of Paediatrics and Child Health in the UK has published a case definition, as well as guidance on how to manage these patients. Management is mainly supportive and involves a multidisciplinary team (paediatric infectious disease, cardiology, rheumatology, critical care).<a href="#">[780]</a> The World Health Organization and the US Centers for Disease Control and Prevention have also published case definitions.<a href="#">[781]</a> <a href="#">[782]</a></p> <p>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. 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.<a href="#">[783]</a></p>		

Complications	Timeframe	Likelihood
Also known as multisystem inflammatory syndrome in children (MIS-C), paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), as well as other variations.		
<b>septic shock</b>	<b>short term</b>	<b>low</b>
<p>Reported in 4% to 8% of patients in case series.[28] [29] [367] [784]</p> <p>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) 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] [448] 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]</p>		
<b>disseminated intravascular coagulation</b>	<b>short term</b>	<b>low</b>
<p>Reported in 71% of non-survivors.[785] 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.[786]</p> <p>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.[787]</p> <p>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.[788] 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 <math>\geq 4</math> or a markedly elevated D-dimer level.[789] In patients with heparin-induced thrombocytopenia (or a history of it), argatroban or bivalirudin are recommended.[786]</p> <p>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.[787] [788]</p>		
<b>acute respiratory failure</b>	<b>short term</b>	<b>low</b>
<p>Reported in 8% of patients in case series.[29]</p> <p>Leading cause of mortality in patients with COVID-19.[662]</p> <p>Children can quickly progress to respiratory failure.[8]</p>		
<b>pregnancy-related complications</b>	<b>short term</b>	<b>low</b>
<p>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, premature labour, 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,</p>		

Complications	Timeframe	Likelihood
<p>preterm birth, and neonatal death. It is unclear whether this is related to COVID-19.[527] [790] [791] [792] [793] [794] [795] [796] [797] [798] [799]</p> <p>Approximately 3% of pregnant women require intensive care admission. The preterm birth rate is 20%, and the neonatal death rate is 0.3%.[800] 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.[18] In Spain, severe adverse maternal outcomes occurred in 11% of pregnant women, and caesarean delivery was independently associated with an increased risk of maternal clinical deterioration and neonatal intensive care unit admission.[801]</p>		
<b>aspergillosis</b>	<b>short term</b>	<b>low</b>
<p>Invasive pulmonary aspergillosis has been reported in critically ill patients with moderate to severe ARDS.[802] [803] [804] A prospective observational study found that one third of mechanically ventilated patients with COVID-19 had putative invasive pulmonary aspergillosis.[805]</p> <p>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.[484] [806]</p> <p>Prescribe appropriate antifungal therapy according to local guidelines.[807]</p>		
<b>pancreatic injury</b>	<b>short term</b>	<b>low</b>
<p>Mild pancreatic injury (defined as elevated serum amylase or lipase levels) has been reported in 17% of patients in one case series. It is unknown whether this is a direct viral effect or due to the harmful immune response that occurs in some patients. Further research is required.[808]</p>		
<b>rhabdomyolysis</b>	<b>short term</b>	<b>low</b>
<p>There have been case reports of rhabdomyolysis in adults and children.[809] [810]</p>		
<b>autoimmune haemolytic anaemia</b>	<b>short term</b>	<b>low</b>
<p>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.[811]</p>		
<b>immune thrombocytopenia</b>	<b>short term</b>	<b>low</b>
<p>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.[812] [813] [814]</p>		
<b>subacute thyroiditis</b>	<b>short term</b>	<b>low</b>
<p>The first known case of subacute thyroiditis has been reported in an 18-year-old woman after SARS-CoV-2 infection. Subacute thyroiditis is a thyroid disease of viral or post-viral origin.[815]</p>		

# 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 5.2% based on World Health Organization data as of 25 June 2020. The CFR varies considerably between countries; for example, it is currently higher in countries such as the UK, France, Italy, and Spain, and significantly lower in countries such as Russia, the US, Germany, Australia, Turkey, Iceland, and Singapore.<sup>[639]</sup>

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).<sup>[4]</sup> 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).<sup>[640]</sup>

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%.<sup>[641]</sup> [\[Centre for Evidence-Based Medicine: global COVID-19 case fatality rates\]](#)

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.<sup>[642]</sup>

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.<sup>[641]</sup> <sup>[643]</sup>

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%).<sup>[28]</sup> Despite the lower CFR, COVID-19 has so far resulted in more deaths than both SARS and MERS combined.<sup>[644]</sup>

## 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.

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.[645]

Evidence is now emerging from seroprevalence studies 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. However, these studies have not been peer reviewed as yet, and may have limitations. Nevertheless, these studies indicate that the IFR may be much lower than the current CFRs.

- Switzerland: seroprevalence data from Geneva indicate an IFR of 0.6% for the total population, and an IFR of 5.6% for people aged 65 years and older (preprint study).[646]
- 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%.[647]
- Denmark: a seroprevalence study in blood donors estimates the IFR to be approximately 0.08% in people aged under 70 years.[648]
- New York: based on results of the first round of testing, a research team estimates that approximately 13.9% of the county's adult population has antibodies to the virus, an estimated IFR of 0.5% based on current deaths in the county.[649]
- 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.[650] Published seroprevalence data from adults in Los Angeles county found that the community prevalence of severe acute respiratory syndrome coronavirus 2 (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.[651]
- 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.[652]
- Germany: the overall seroprevalence in healthcare workers in a tertiary hospital was low (1.6%).[653]
- Iceland: the country where the most testing per capita has occurred - the IFR lies between 0.01% and 0.19%.[641]
- China: seropositivity varied between 3.2% and 3.8% in Wuhan, and decreased in other Chinese cities as the distance to the epicentre increased.[654]

These estimates are likely to change as more data emerge.

The Centers for Disease Control and Prevention's current best estimate of the overall CFR in symptomatic cases is 0.4%. It projects a 35% rate of asymptomatic cases among those infected, which makes the IFR approximately 0.26%.[655]

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

The CFR increases with age.[640] 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.[656]

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.[640]

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.[657] 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%.<sup>[658]</sup>

In the US, the CFR was highest among patients aged  $\geq 85$  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  $\leq 19$  years (no deaths). Patients aged  $\geq 65$  years accounted for 80% of deaths.<sup>[7]</sup> 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.<sup>[659]</sup> The CFR in residents in a long-term care facility in Washington was reported to be 34%.<sup>[660]</sup>

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.<sup>[661]</sup>

Children have a good prognosis and generally recover within 1 to 2 weeks, and deaths are rare.<sup>[17]</sup>

## Prognostic factors

The leading cause of death in patients with COVID-19 is respiratory failure from acute respiratory distress syndrome.<sup>[662]</sup> 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.<sup>[155] [156] [663]</sup> The other most common complications in deceased patients are myocardial injury, liver or kidney injury, and multi-organ dysfunction.<sup>[664]</sup> 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.<sup>[152]</sup> 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.<sup>[665]</sup>

Prognostic factors that have been associated with disease progression to severe or critical illness or even death include:<sup>[109] [147] [156] [379] [399] [666] [667] [668] [669] [670] [671] [672] [673] [674] [675]</sup>

- Age  $\geq 65$  years
- Male sex
- Smoking
- Presence of comorbidities (e.g., hypertension, diabetes, cardiovascular or cerebrovascular disease, respiratory disease, obesity)
- Dyspnoea
- Hypoxaemia
- Higher respiratory rate
- Lymphopenia
- Leukocytosis
- Thrombocytopenia
- High neutrophil-to-lymphocyte ratio
- Decreased albumin level
- Hyperglycaemia
- Liver or kidney impairment
- Elevated lactate dehydrogenase
- Elevated inflammatory markers (C-reactive protein, procalcitonin)
- Elevated cardiac troponin I
- Elevated D-dimer
- Elevated serum amyloid A
- Decreased CD3+, CD4+, or CD8+ T cells
- Elevated interleukin-6
- Elevated serum cortisol

- Higher Sequential Organ Failure Assessment (SOFA) or Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

The most common risk factors for death are age  $\geq 65$  years, male sex, hypertension, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, and cancer.<sup>[676]</sup>

## 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.<sup>[669]</sup> 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).<sup>[677]</sup> <sup>[678]</sup> 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 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.<sup>[678]</sup>

## 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.<sup>[679]</sup>

## 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.<sup>[680]</sup> <sup>[681]</sup>

## 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.<sup>[682]</sup> <sup>[683]</sup> <sup>[684]</sup> <sup>[685]</sup> <sup>[686]</sup> <sup>[687]</sup> 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.<sup>[688]</sup> 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.<sup>[689]</sup> 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.<sup>[690]</sup> Further research is required.

## Post-infection immunity

Most convalescent patients have detectable neutralising antibodies and cellular immune responses.<sup>[691]</sup> A study in macaques suggests that infection with SARS-CoV-2 offers protection against reinfection.<sup>[692]</sup> 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.<sup>[693]</sup> There are data to suggest that asymptomatic people may have a weaker immune response to infection; however, this is yet to be confirmed.<sup>[694]</sup>



## Recovery

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).<sup>[695]</sup>

# Diagnostic guidelines

## Europe

### 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

### Global surveillance for COVID-19 caused by human infection with COVID-19 virus

**Published by:** World Health Organization

**Last published:** 2020

### Infection prevention and control during health care when COVID-19 is suspected

**Published by:** World Health Organization

**Last published:** 2020

### Use of chest imaging in COVID-19

**Published by:** World Health Organization

**Last published:** 2020

## 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 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

## 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

# Treatment guidelines

## Europe

### Coronavirus specialty guides

**Published by:** NHS England

**Last published:** 2020

### 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

### 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

## International

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

**Published by:** World Health Organization

**Last published:** 2020

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

**Published by:** World Health Organization

**Last published:** 2020

### Home care for patients with COVID-19 presenting with mild symptoms 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

### 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

## North America

### Coronavirus disease 2019 (COVID-19) treatment guidelines

**Published by:** National Institutes of Health

**Last published:** 2020

### 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

**Published by:** Infectious Diseases Society of America

**Last published:** 2020

### Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19

**Published by:** CHEST Guideline and Expert Panel

**Last published:** 2020

## North America

### Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the Anticoagulation Forum

**Published by:** Anticoagulation Forum

**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



## Asia

### 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

## Oceania

### Coronavirus disease 2019 (COVID-19)

**Published by:** Department of Health Australia

**Last published:** 2020

## Online resources

1. [Johns Hopkins University: coronavirus COVID-19 global cases](#) (*external link*)
2. [BMJ talk medicine podcast: Covid-19 update](#) (*external link*)
3. [BMJ Best Practice: Management of co-existing conditions in the context of COVID-19](#) (*external link*)
4. [WHO: coronavirus disease \(COVID-19\) emergency dashboard](#) (*external link*)
5. [WHO: coronavirus disease \(COVID-2019\) situation reports](#) (*external link*)
6. [CDC: coronavirus disease 2019 \(COVID-19\) – cases in the US](#) (*external link*)
7. [CDC: COVIDView](#) (*external link*)
8. [GenBank](#) (*external link*)
9. [WHO: infection prevention and control during health care when COVID-19 is suspected](#) (*external link*)
10. [CDC: interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 \(COVID-19\) pandemic](#) (*external link*)
11. [CDC: strategies to optimize the supply of PPE and equipment](#) (*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. [PHE: 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*)
22. [Public Health England: guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19](#) (*external link*)

23. [Royal College of Paediatrics and Child Health: COVID-19 – ‘shielding’ guidance for children and young people \(external link\)](#)
24. [PHE: COVID-19 – advice for smokers and vapers \(external link\)](#)
25. [BSTI: radiology decision tool for suspected COVID-19 \(external link\)](#)
26. [BSTI: lung ultrasound \(LUS\) for COVID-19 patients in critical care areas \(external link\)](#)
27. [WHO: global surveillance for COVID-19 caused by human infection with COVID-19 virus \(external link\)](#)
28. [WHO: home care for patients with COVID-19 presenting with mild symptoms and management of their contacts \(external link\)](#)
29. [CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 \(COVID-19\) \(external link\)](#)
30. [Clinical frailty scale \(external link\)](#)
31. [ACOG: outpatient assessment and management for pregnant women with suspected or confirmed novel coronavirus \(COVID-19\) \(external link\)](#)
32. [Global coronavirus COVID-19 clinical trial tracker \(external link\)](#)
33. [WHO: off-label use of medicines for COVID-19 \(external link\)](#)
34. [RECOVERY trial \(external link\)](#)
35. [Centre for Evidence-Based Medicine: hydroxychloroquine for COVID-19 – what do the clinical trials tell us? \(external link\)](#)
36. [Centre for Evidence-Based Medicine: lopinavir/ritonavir – a rapid review of effectiveness in COVID-19 \(external link\)](#)
37. [Centre for Evidence-Based Medicine: global COVID-19 case fatality rates \(external link\)](#)
38. [NHS England: acute kidney injury \(AKI\) algorithm \(external link\)](#)
39. [WHO: coronavirus disease \(COVID-19\) advice for the public – when and how to use masks \(external link\)](#)
40. [Public Health England: how to wear and make a cloth face covering \(external link\)](#)
41. [CDC: use of cloth face coverings to help slow the spread of COVID-19 \(includes instructions on how to make masks\) \(external link\)](#)
42. [WHO: coronavirus disease \(COVID-19\) travel advice \(external link\)](#)

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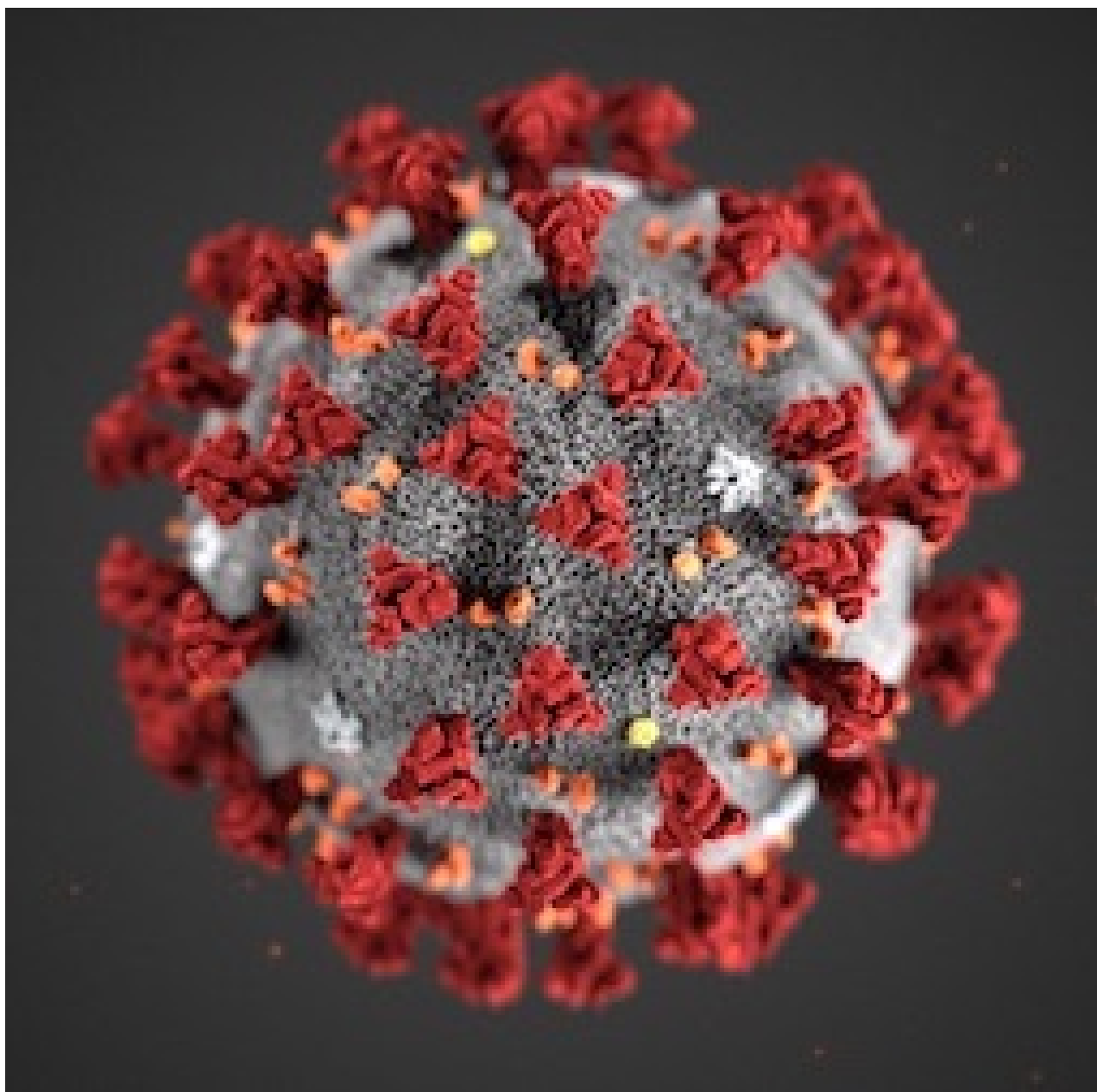
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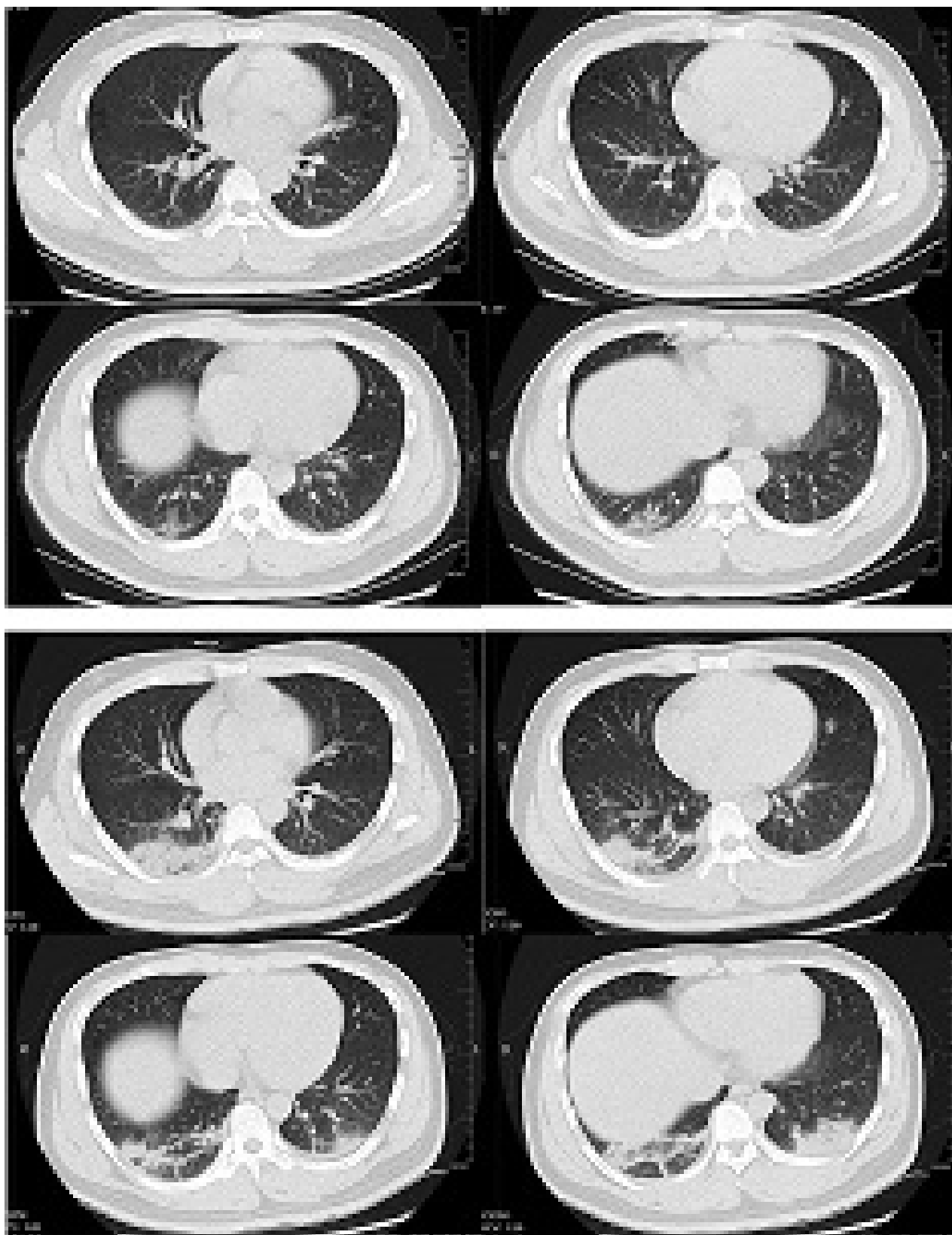
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## Images



*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*

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