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 declared the COVID-19 outbreak a pandemic on 11 March 2020. The situation is evolving rapidly. Clinical trials and investigations to learn more about the virus, its origin, and how it affects humans are ongoing.

# Definition

Coronavirus disease 2019 (COVID-19) is a potentially severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The virus was identified as the cause of an outbreak of pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019.[2] The clinical presentation is 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.

# Epidemiology

The World Health Organization (WHO) was informed of 44 cases of pneumonia of unknown microbial aetiology associated with Wuhan City, Hubei Province, China on 31 December 2019. Most of the patients in the outbreak reported a link to a large seafood and live animal market (Huanan South China Seafood Market).[4] The WHO announced that a novel coronavirus had been detected in samples taken from these patients. Laboratory tests ruled out severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS)-CoV, influenza, avian influenza, and other common respiratory pathogens.[5] Since then, the outbreak has escalated rapidly, 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.

Consult the resources below for updated information on daily case counts:

- [Johns Hopkins University: coronavirus COVID-19 global cases]
- [WHO: coronavirus disease (COVID-19) emergency dashboard]
- [WHO: coronavirus disease (COVID-2019) situation reports]
- [CDC: cases of coronavirus disease (COVID-19) in the US]
- [CDC: COVIDView]

Data from the largest case series in China found that 87% of confirmed cases were aged 30 to 79 years, 1% were aged 9 years or younger, 1% were aged 10 to 19 years, and 3% were aged 80 years or older. Approximately 51% of patients were male and 49% were female.[7] Approximately 4% of cases were in healthcare workers, with 23 deaths reported.[8]

Early data from a small retrospective study in Italy found the median age and prevalence of comorbidities to be higher in this population compared with the studies from China.[9]

In the US, older patients (aged ≥65 years) accounted for 31% of all cases, 45% of hospitalisations, 53% of intensive care unit admissions, and 80% of deaths, with the highest incidence of severe outcomes in patients aged ≥85 years.[10]

Infection in children is reported much less commonly than among adults. A systematic review found that children account for only 1% to 5% of confirmed cases (depending on the country).[11] In the US, children accounted for only 1.7% of all cases.[12] All cases have been in family clusters or in children who have a history of close contact with an infected patient.[13] [14] [15] In a case series of 2143 paediatric patients in China, the median age of children was 7 years.[16] Unlike adults, children do not seem to be at higher risk for severe illness based on age or sex.[17]

Emerging evidence suggests that weather conditions may influence the transmission of COVID-19, with cold and dry conditions appearing to increase transmission.[18] [19] Higher latitude may also be associated with an increased risk of cases and deaths in some countries.[20] However, other data suggest that ambient temperature has no significant impact on transmission.[21] Further research is required on how weather conditions influence transmission as colder temperatures have been associated with increased transmission of other coronaviruses.

# 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.[2] 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.[22] [23] 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.[24]

[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.[25] [26] [27]
- 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.[22] [23] [28] [29] Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses.[30] [31]

Transmission dynamics

- Person-to-person spread has been confirmed in community and healthcare settings, with local transmission occurring 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.[27]

- 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 via contact with fomites. Airborne transmission has not been reported; however, it may be possible during aerosol-generating procedures performed in clinical care.[25] [27] [32] [33]
- 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).[34] This study also found that the virus was viable in aerosol particles for up to 3 hours; however, aerosols were generated using high-powered apparatus that do not reflect normal human cough conditions or a clinical setting where aerosol-generating procedures are performed. The World Health Organization has confirmed that there have been no reports of airborne transmission.[35] 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.[36]
- 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, urine, saliva, tears, and conjunctival secretions. Faecal-oral transmission may be possible (virus has been detected in the stool samples of almost half of the patients in one meta-analysis), although it has not been reported yet.[37] [38] [39] [40] [41] [42] [43] Patients with diarrhoea are more likely to have viral RNA in their stool.[44] The presence of virus in these fluids or viral RNA shedding does not necessarily equate with infectivity.
- Nosocomial transmission in healthcare workers and patients has been reported in 41% of patients in one case series.[45] 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.[46] Screening of healthcare workers in a hospital trust in the UK found that 14% of healthcare workers tested positive.[47]
- Widespread transmission has been reported in long-term care facilities, homeless shelters, and prisons, and on cruise ships (19% of 3700 passengers and crew were infected aboard the Diamond Princess).[48] [49] [50] [51] [52]
- Clusters of cases originating from family gatherings have been reported, emphasising the importance of social distancing even within families.[53]
- Clusters of cases originating from mass gatherings have been reported; for example, approximately 8% of attendees of the Sri Petaling gathering (Moslem missionary movement) in Kuala Lumpur tested positive.[54]
- The secondary attack rate among all close contacts is approximately 0.45%.[33] The secondary attack rate among household members is 10% to 30%.[33] [55] [56] 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.[56]

Presymptomatic transmission

- A small number of studies suggest that some people can be contagious during the incubation period, the time between exposure to the virus and the onset of symptoms. The incubation period is estimated

to be between 1 and 14 days, with a median of 5 to 7 days (possibly longer in children). Approximately 97.5% of patients develop symptoms within 11.5 days of infection.[57] [58] [59] [60] [61]

- Presymptomatic transmission has been reported in 12.6% of cases in China.[62] 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.[63]
- Presymptomatic transmission still requires the virus to be spread by infectious droplets or contact with fomites.

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).[64] [65] [66] [67] [68] [69] [70]
- 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.[71] However, a Japanese study of citizens evacuated from Wuhan City estimates the rate to be closer to 31%.[72] Early data from an isolated village of 3000 people in Italy estimates the figure to be higher at 50% to 75%.[73] Other studies ranged from 4% to 80%.[74]
- 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.[75] 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.[76]
- Asymptomatic (or paucisymptomatic) transmission has been reported in family clusters.[77]
- A 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.[78]
- The proportion of asymptomatic cases in children is thought to be significant, and children may play a role in community spread.[79] 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.[80]

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.[81]
- 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.[82] [83]
- 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.[82]

Perinatal transmission

- It is unknown whether perinatal transmission (including transmission via breastfeeding) is possible. Retrospective reviews of pregnant women with COVID-19 found that there is no evidence for intrauterine infection in women with COVID-19.[84] [85] [86] However, vertical transmission cannot

 

be ruled out.[87] [88] There have been case reports of infection in neonates born to mothers with COVID-19, and virus-specific antibodies have also been detected in neonatal serum samples.[89] [90] [91] [92] [93]

# Pathophysiology

Reproductive number

- 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.[27] [94] However, the $R_0$ may actually be lower in light of social distancing measures that have been instituted.

Angiotensin-converting enzyme-2 receptor

- While the pathophysiology is currently unknown, it has been confirmed that the virus binds to the angiotensin-converting enzyme-2 (ACE2) receptor in humans, which suggests a similar pathogenesis to SARS.[23] [95] However, 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.[96] A furin-like cleavage site has been identified in the spike protein of the virus; this does not exist in other SARS-like coronaviruses.[97]
- 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.[98]
- Mechanistic evidence from other coronaviruses suggests that SARS-CoV-2 may downregulate ACE2, leading to a toxic overaccumulation of angiotensin-II, which may induce acute respiratory distress syndrome and fulminant myocarditis.[99]

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.[100] [101] High viral load at baseline may be associated with more severe disease and risk of disease progression.[102]
- 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.[103]
- 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. It is unclear whether the virus is capable of transmission later in the course of the disease.[104] [105] [106] [107] [108] Viral shedding continued until death in non-survivors.[104]
- 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.[109]
- 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. The median duration of shedding was lower in mild illness (14 days) compared with severe illness (21 days).[110]

# Classification

## World Health Organization: clinical classification of COVID-19[3]

Mild illness

- Patients with uncomplicated upper respiratory tract viral infection may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnoea, nasal congestion, or headache. Rarely, patients may also present with diarrhoea, nausea, and vomiting.
- Older and/or immunosuppressed patients may present with atypical symptoms.
- Symptoms due to physiological adaptations of pregnancy or adverse pregnancy events (e.g., dyspnoea, fever, gastrointestinal symptoms, fatigue) may overlap with COVID-19 symptoms.

Pneumonia

- Adults: pneumonia with no signs of severe pneumonia (see below) and no need for supplemental oxygen.
- Children: pneumonia with cough or difficulty breathing plus fast breathing (i.e., <2 months of age: ≥60 breaths/minute; 2-11 months of age: ≥50 breaths/minute; 1-5 years years of age: ≥40 breaths/minute) and no signs of severe pneumonia (see below).

Severe pneumonia in adults and adolescents

- Fever or suspected respiratory infection plus one of the following:
    - Respiratory rate >30 breaths/minute
    - Severe respiratory distress
    - $SpO_2$ ≤93% on room air.

Severe pneumonia in children

- Cough or difficulty breathing plus at least one of the following:
    - Central cyanosis or $SpO_2$ <90%
    - Severe respiratory distress (e.g., grunting, very severe chest indrawing)
    - Signs of pneumonia with a general danger sign (i.e., inability to breastfeed or drink, lethargy or unconsciousness, or convulsions).
- Other signs of pneumonia may be present in children including chest indrawing or fast breathing (i.e., <2 months of age: ≥60 breaths/minute; 2-11 months of age: ≥50 breaths/minute; 1-5 years years of age: ≥40 breaths/minute).
- While the diagnosis is made on clinical grounds, chest imaging may identify or exclude some pulmonary complications.

 

# Primary prevention

General prevention measures

- The only way to prevent infection is to avoid exposure to the virus and people should be advised to:[143] [144]
    - 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. 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
    - 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 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]

Face masks

- Recommendations on the use of face masks in community settings vary between countries.[145] It is mandatory to wear a mask in public in certain countries, and masks may be worn in some countries according to local cultural habits. Consult local guidance for more information.
- The World Health Organization recommends that medical masks should be reserved for healthcare workers. People with symptoms should also wear a medical mask, self-isolate, and seek medical advice as soon as possible. Masks are also recommended for those caring for a sick person at home when in the same room. There is currently no evidence that wearing a mask (medical or other types) in the community setting can prevent infection with respiratory viruses, including COVID-19, in a healthy person.[146]
- 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.[147] However, there is no evidence to support this.[148]
- 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.[146] [149]
- 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.[150] A small study found that surgical and cotton masks are ineffective at preventing viral spread to the environment from the cough of patients with COVID-19.[151]

- [BMJ: facemasks for the prevention of infection in healthcare and community settings]
- [BMJ: analysis - face masks for the public during the covid-19 crisis]
- [WHO: coronavirus disease (COVID-19) advice for the public - when and how to use masks]

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.[152] 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.[153]
- 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).[154] The psychosocial effects of enforced quarantine may have long-lasting repercussions.[155] [156] 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.[157]

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.[158] [159]
- 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.[160]
- [Public Health England: guidance on social distancing for everyone in the UK]

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:[161]
    - Solid organ transplant recipients
    - People with specific cancers
    - People with severe respiratory conditions (e.g., cystic fibrosis, severe asthma, or COPD)
    - People with rare diseases or inborn errors of metabolism that 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).
- These groups are advised to stay at home at all times, and avoid any face-to-face contact for a period of at least 12 weeks (this time period is subject to change). Visits from people who provide essential



 

support should continue provided these people do not have symptoms and follow hand hygiene measures.
- 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]

Vaccine

- There is currently no vaccine available. Vaccines are in development, but it may take at least 12 to 18 months before one is available. Seven vaccine candidates are currently approved for human testing through clinical trials, including mRNA and DNA platform vaccines, adenovirus vector vaccines, and an inactivated virus vaccine.[162] Vaccines are being fast-tracked and skipping the animal testing stage.

Smoking cessation

- Past or current smokers have double the risk for severe disease, and smoking cessation should be encouraged.[128]



# 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:[270]

- 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.[271] 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.[272]

## 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.[273]

# Secondary prevention

Early recognition of new cases is the cornerstone of prevention of transmission. Immediately isolate all suspected and confirmed cases and implement recommended infection prevention and control procedures according to local protocols, including standard precautions at all times, and contact, droplet, and airborne precautions while the patient is symptomatic.[165] COVID-19 is a notifiable disease; report all suspected and confirmed cases to your local health authorities.

Detailed guidance on infection prevention and control measures are available from the World Health Organization and the Centers for Disease Control and Prevention:

- [WHO: infection prevention and control during health care when COVID-19 is suspected]
- [CDC: interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings]

# 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 and his temperature is 38.7°C (101.6°F). He is admitted to hospital in an isolation room and is started on oxygen, intravenous fluids, empirical antibiotics, and paracetamol. 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 and who live in or report a travel history to an area with local transmission or close contact with a suspected or confirmed case in the 14 days prior to symptom onset. Evaluation should be performed according to pneumonia severity indexes and sepsis guidelines (if sepsis is suspected) in all patients with severe illness.

It is important that general practitioners avoid in-person assessment of patients with suspected COVID-19 in primary care when possible.[163] Most patients can be managed remotely by telephone or video consultations.[164] Algorithms for dealing with these patients are available:

- [BMJ: covid-19 in primary care (UK)]
- [BMJ: covid-19 - a remote assessment in primary care]

## Infection prevention and control

Triage all patients on admission and immediately isolate all suspected and confirmed cases in an area separate from other patients. Suspected patients should be given a mask and kept at least 1 metre (3 feet) from other suspected patients. It is important to note that recommended distances differ between countries and you should consult local guidance. Implement appropriate infection prevention and control procedures. Screening questionnaires may be helpful. COVID-19 is a notifiable disease; report all suspected and confirmed cases to your local health authorities.

[BMJ: covid-19 - PPE guidance]

The World Health Organization (WHO) recommends the following basic principles:[165]

- Immediately isolate all suspected cases in an area that is separate from other patients
- Implement standard precautions at all times:
    - 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:
    - 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
- All specimens collected for laboratory investigations should be regarded as potentially infectious.

Some countries and organisations recommend airborne precautions for any situation involving the care of a COVID-19 patient.

It is important to disinfect inanimate surfaces in the surgery or hospital as patients may touch and contaminate surfaces such as door handles and desktops.[166]

Detailed guidance on infection prevention and control procedures are available from the WHO and the Centers for Disease Control and Prevention (CDC):

- [WHO: infection prevention and control during health care when COVID-19 is suspected]
- [CDC: interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings]
- [CDC: strategies to optimize the supply of PPE and equipment]

## 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, smoking history, and presence of any underlying health conditions.



 

Diagnosis should be suspected in:[111]

- 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 our Diagnostic criteria section for full case definitions.

## Clinical presentation

The clinical presentation resembles viral pneumonia, and the severity of illness ranges from mild to severe. Approximately 80% of patients present with mild illness, 14% present with severe illness, and 5% present with critical illness.[7] Severe illness is associated with older age and the presence of underlying health conditions.[7] [112] Older patients and/or those with comorbidities may present with mild symptoms, but have a high risk of deterioration.[3] Atypical presentations may occur, especially in older patients (e.g., falls, delirium, confusion, functional decline) or patients who are immunocompromised. Persistent hiccups have been reported as the presenting complaint in one older patient.[167]

Approximately 5% of patients with a mild influenza-like illness (and no risk factors for COVID-19) who presented to a Los Angeles emergency department tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), although this study was limited by the brief sampling period at one medical centre.[168]

The most common symptoms are:[25] [26] [45] [169] [170] [171]

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

Less common symptoms include:

- Anorexia
- Sputum production
- Gastrointestinal symptoms
- Sore throat
- Confusion
- Dizziness
- Headache
- Rhinorrhoea or nasal congestion
- Haemoptysis
- Chest pain
- Conjunctivitis
- Cutaneous manifestations.

Approximately 90% of patients present with more than one symptom, and 15% of patients present with fever, cough, and dyspnoea.[26] Some patients may be minimally symptomatic or asymptomatic. Mild illness is defined as patients with an uncomplicated upper respiratory tract infection with non-specific symptoms such as fever, cough (with or without sputum production), fatigue, anorexia, malaise, myalgia, sore throat, dyspnoea, nasal congestion, or headache. Patients may have gastrointestinal symptoms. The most common diagnosis in patients with severe COVID-19 is severe pneumonia.[3]

Initial impressions from cases in 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.[172] Data from the first 393 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.[122]

A retrospective case series of 62 patients in Zhejiang province found that the clinical features were less severe than those of the primary infected patients from Wuhan City, indicating that second-generation infection may result in milder infection. This phenomenon was also reported with Middle East respiratory syndrome.[173]

Co-infections have been reported. In a sample of approximately 1200 patients with respiratory symptoms, 21% of nasopharyngeal swab specimens that tested positive for SARS-CoV-2 also tested positive for other respiratory pathogens, most commonly rhinovirus/enterovirus, respiratory syncytial virus, and non-SARS-CoV-2 *Coronaviridae* .[174] Patients with influenza co-infection showed similar characteristics to those patients with COVID-19 only.[104] [175] [176] In another study of 5700 patients in New York, 2% of patients had a co-infection.[115]

## 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.

## 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.

Children are typically asymptomatic or present with mild symptoms (e.g., fever, cough, fatigue, rhinorrhoea, nasal congestion). Some children may present with fever and no respiratory symptoms. Respiratory symptoms are generally mild when present. Children may also present with gastrointestinal symptoms, particularly newborns and infants. Severe disease has been reported rarely.[17] [177] In a study of 2143 paediatric patients in China, over 90% of children were asymptomatic or had a mild or moderate illness; 16% were asymptomatic and had no radiological evidence of pneumonia.[16]

There is increasing concern that a related inflammatory syndrome is emerging in children with severe disease. The UK's Paediatric Intensive Care Society has reported a very small number of cases of a novel multisystem inflammatory state in children of all ages over the last few weeks. Some of these patients tested positive for COVID-19, while some did not. The society has warned clinicians to be



 

vigilant for children presenting with overlapping signs of Kawasaki disease and toxic shock syndrome and blood work consistent with COVID-19 (e.g., elevated C-reactive protein, elevated serum ferritin, elevated erythrocyte sedimentation rate). Common features include abdominal pain, other gastrointestinal symptoms, and cardiac inflammation (elevated troponin and pro-B-type natriuretic peptide levels). However, the society notes that there may be another as yet unidentified infectious pathogen associated with these cases.[178] [179]

Cases of COVID-19 have been reported in neonates. Although illness is usually mild, late-onset neonatal sepsis has been reported in one case.[180] Infants may present with irritability, crying, and neurological symptoms.[181]

Co-infections may be more common in children.[182] It is unknown whether children with underlying health conditions are more at risk of severe illness. Complications in children appear to be milder and more rare.

## Pregnant women

Retrospective reviews of pregnant women with COVID-19 found that the clinical characteristics in pregnant women were similar to those reported for non-pregnant adults.[84] [90] It is important to note that symptoms such as fever, dyspnoea, and fatigue may overlap with symptoms due to physiological adaptations of pregnancy or adverse pregnancy events.[3]

## Initial investigations

Order the following investigations in all patients with severe illness:

- Pulse oximetry
- ABG (as indicated to detect hypercarbia or acidosis)
- FBC
- Comprehensive metabolic panel
- Coagulation screen
- Inflammatory markers (e.g., serum procalcitonin, C-reactive protein, and ferritin)
- Serum troponin
- Serum lactate dehydrogenase
- Serum creatine kinase.

The most common laboratory abnormalities in patients hospitalised with pneumonia include leukopenia, lymphopenia, leukocytosis, thrombocytopenia, elevated liver transaminases, elevated lactate dehydrogenase, and elevated C-reactive protein and other inflammatory markers. Other abnormalities include neutrophilia, decreased haemoglobin, decreased albumin, and renal impairment.[25] [26] [45] [171] [122] [183]

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

## Pulse oximetry

Pulse oximetry may reveal low oxygen saturation ($SpO_2$ <90%).

Clinicians should be aware that patients with COVID-19 can develop ‘silent hypoxia': their oxygen saturations can drop to low levels and precipitate acute respiratory failure without the presence of obvious symptoms of respiratory distress. Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognising further

deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[184]

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.[185]

## Blood and sputum cultures

Collect blood and sputum specimens for culture in all patients 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.[3]

## 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. The WHO recommends prioritising people with a likelihood of infection. Consider testing asymptomatic or mildly symptomatic contacts of confirmed COVID-19 cases. Symptomatic pregnant women should also be prioritised in order to enable access to specialised care.[3] Consult local health authorities for guidance as testing priorities will depend on local guidelines and available resources. See our Criteria section for CDC and Infectious Diseases Society of America recommendations on testing priorities.

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.[186]

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

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, additional specimens should be collected and tested, especially if only upper respiratory tract specimens were collected initially.[186] 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.[187]

Collect nasopharyngeal swabs for testing to rule out infection with other respiratory pathogens (e.g., influenza, atypical pathogens) 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.[3] [188]



 

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 does not recommend the use of these tests outside of research settings as they have not been validated as yet.[189] Antibody responses to SARS-CoV-2 typically occur during the first 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.[127] [190] Serum samples can be stored to retrospectively define cases when validated serology tests become available.

## Chest x-ray

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.[191]

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.[25] [26] [192]

## Computed tomography

Consider ordering a computed tomography (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.[193]

[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.[194]

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.[195]

Abnormal chest CT findings have been reported in up to 97% of COVID-19 patients in one meta-analysis of 50,466 hospitalised patients.[170] Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[196] CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients.[67] [197] Some patients may present with a normal chest finding despite a positive RT-PCR.[198] 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.[199]

Typical features

- Multiple bilateral lobular and subsegmental areas of ground-glass opacity or consolidation are seen in most patients, usually with a peripheral or posterior distribution, mainly in the lower lobes

and less frequently in the right lower lobe. Consolidative opacities superimposed on ground-glass opacity may be found in a smaller number of cases, usually older patients.[25] [173] [200]

- Other classic findings include crazy-paving pattern, air bronchograms, and a reverse halo/perilobular pattern (i.e., organising pneumonia patterns).[193]
- 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.[201]
- Older people are more likely to have extensive lung lobe involvement, interstitial changes, and pleural thickening compared with younger patients.[202]
- Children may have signs of pneumonia on chest imaging despite having minimal or no symptoms.[182] Small nodular ground-glass opacities and consolidation with surrounding halo signs are typical in children.[182] [203] Children tend to have more localised ground-glass opacity, lower ground-glass opacity attenuation, and relatively rare interlobular septal thickening.[204]

Atypical features

- Interlobular or septal thickening (smooth or irregular), thickening of the adjacent pleura, and subpleural involvement are atypical features. Some patients may rarely present with pleural effusion, pericardial effusion, bronchiectasis, cavitation, pneumothorax, lymphadenopathy, and round cystic changes. Atypical features appear to be more common in the later stages of disease, or on disease progression.[25] [173] [200]

Disease progression

- Abnormalities can rapidly evolve from focal unilateral to diffuse bilateral ground-glass opacities that progress to, or co-exist with, consolidations within 1 to 3 weeks.[197]
- The greatest severity of CT findings is usually visible around day 10 after symptom onset, and imaging signs associated with clinical improvement (e.g., resolution of consolidative opacities, reduction in number of lesions and involved lobes) usually occur after week 2 of the disease.[200]

Sensitivity of CT

- In a cohort of over 1000 patients in a hyperendemic area in China, chest CT had a higher sensitivity for diagnosis of COVID-19 compared with initial RT-PCR from swab samples (88% versus 59%). Improvement of abnormal CT findings also preceded change from RT-PCR positivity to negativity in this cohort during recovery. The sensitivity of chest CT was 97% in patients who ultimately had positive RT-PCR results. However, in this setting, 75% of patients with negative RT-PCR results also had positive chest CT findings. Of these patients, 48% were considered highly likely cases, while 33% were considered probable cases.[205]

## Lung ultrasound

There is emerging evidence that lung ultrasound may be a useful aid in the diagnosis of COVID-19 as it has high sensitivity for detecting pleural thickening, subpleural consolidation, and ground-glass opacity. It has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, and repeatability during follow-up. However, it also has limitations (e.g., it is unable to discern chronicity of a lesion) and other imaging modalities may be required. Characteristic ultrasound patterns have been reported in patients with COVID-19 and include B-lines, white lung, pleural line thickening, and consolidations with air bronchograms.[206] [207] [208] [209] Ultrasound also appears to be a useful imaging modality in children.[210]



 

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

# Risk factors

## Strong

### residence in/travel to location reporting community transmission during the 14 days prior to symptom onset

- 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.[111]

### 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.[111]

### older age and/or underlying health conditions

- People aged 65 years and older, those who live in a nursing home or long-term care facility, and those with a high-risk condition (e.g., chronic respiratory disease, cardiovascular disease, immunocompromised, severe obesity, diabetes, hypertension, renal or liver disease) are at higher risk for severe illness.[112] [113]
- The most prevalent comorbidities in patients with COVID-19 in China were hypertension, cardiovascular disease, diabetes, smoking, respiratory disease such as COPD, malignancy, and chronic kidney disease.[114] The most prevalent comorbidities in 5700 patients in New York were hypertension (57%), obesity (42%), and diabetes (34%).[115]
- 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 cardiovascular disease, diabetes, respiratory disease, hypertension, or cancer. The risk is lower in people ages 18 to 29 years (approximately 20%), and higher in people ages 80 years and older (81%). Risk varies by race/ethnicity, state, employment, and health insurance.[116]
- Diabetes is associated with increased risk of mortality, severe disease, disease progression, and acute respiratory distress syndrome.[117]

### obesity

- Obesity is a common risk factor in both younger and older people. These patients are at higher risk of severe disease and intensive care admission.[118] [119] [120] Data from 5700 hospitalised patients in New York found that 42% of patients had obesity, and this may be a risk factor for respiratory failure leading to invasive mechanical ventilation.[115] It is thought that COVID-19 may affect younger people in populations with a higher prevalence of obesity.[121]

### male sex

- Male sex appears to be a risk factor for severe disease, disease progression, need for mechanical ventilation, and increased mortality.[122] [123] The case fatality rate in China was higher in males compared with females (2.8% versus 1.7% for females).[7]

### smoking

- Smoking has been associated with more severe disease, adverse outcomes, and a poorer prognosis.[124] [125] [126] However, there are also epidemiological data that show no significant association between current smoking and severe disease.[127] Past or current smokers with COVID-19 have double the risk for severe disease outcomes (18%) compared with people who have never smoked (9%) according to a preprint (not peer reviewed) meta-analysis of 9000 patients.[128] This may be due to increased airway expression of the angiotensin-converting enzyme-2 receptor in smokers.[129] [130]
- While current data on the role of smoking in COVID-19 are inconclusive, smoking is a known risk factor for acute respiratory infections in general, including both the smoker and the people around them.[131]

### malignancy

- Patients with cancer are thought to be at a higher risk of contracting COVID-19 because treatments such as radiotherapy and chemotherapy are immunosuppressive, and patients with cancer are often in hospital for treatment and monitoring and so may be at risk of nosocomial infection.
- A retrospective study of 1524 patients at a single institution in Wuhan City, China, found that the infection rate in patients with cancer was higher than the cumulative incidence of all diagnosed cases reported in the city over the same period of time (i.e., 0.79% versus 0.37%). However, fewer than half of these infected patients were undergoing active treatment, suggesting that recurrent hospital visits and admissions were a potential risk factor.[132]
- A multicentre, retrospective study found that patients with cancer, particularly those with metastatic disease, haematological cancer, or lung cancer, had more severe outcomes (i.e., increased risk of having at least one severe or critical symptom, increased risk of requiring intensive care unit admission or mechanical ventilation, and increased mortality) when compared with patients without cancer. Patients with cancer appeared to deteriorate more quickly compared with those without cancer. Patients who underwent cancer surgery had higher mortality rates and an increased risk of having critical symptoms.[133]
- Data suggest that other immunosuppressed patients are not at an increased risk of severe illness; however, further research is required in these patients.[134]

### organ transplant

- Organ transplant recipients may be at higher risk of severe illness, 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.[135] [136] [137] [138]

### surgery

- Surgery may accelerate and exacerbate disease progression. 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. Further study is required.[139]

### air pollution

- Emerging evidence suggests that there may be an association between long-term exposure to ambient air pollution and severity of COVID-19; however, data is limited.[140] [141] 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.[142]

# History & examination factors

## Key diagnostic factors

### fever (common)

- Reported in 77% to 98% of patients in case series.[25] [26] [45] [211] [170] [171] [212] In one case series, 44% of patients had a fever on presentation, but it developed in 89% of patients after hospitalisation.[169]
- Children may not present with fever, or may have a brief and rapidly resolving fever.[13] [213] [214]
- Patients may present with chills/rigors.
- The course of fever is not fully understood yet, but it may be prolonged and intermittent.

### cough (common)

- Reported in 57% to 82% of patients in case series.[25] [26] [45] [211] [169] [170] [171] [212]
- Less common in children.[213]
- Cough is usually dry.

### dyspnoea (common)

- Reported in 18% to 57% of patients in case series.[25] [26] [45] [211] [169] [171] [212]
- Median time from onset of symptoms to development of dyspnoea is 5 to 8 days.[25] [26] [45]
- Polypnoea has been reported in children with severe illness.[215]

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

- There is evidence that patients with mild to moderate illness may develop an altered sense of smell (anosmia/hyposmia) or taste (ageusia/dysgeusia) as an early symptom and in the absence of other symptoms.[216]
- In a multicentre European study of 417 patients with mild to moderate illness, 86% of patents reported olfactory dysfunction (most patients reported anosmia without nasal obstruction or rhinorrhoea), and 88% of patients reported gustatory dysfunction. Symptoms may appear before, during, or after other COVID-19 symptoms.[217] In another study of 200 patients in Italy, 64% of patients reported a sudden altered sense of smell or taste in the 2 weeks prior to being tested; 35% of these patients also reported a blocked nose.[218] Prevalence of these symptoms in European patients is substantially higher than that reported in China.
- It is possible that these patients may be hidden carriers, but further research is required.[219]
- The American Academy of Otolaryngology - Head and Neck Surgery has proposed adding anosmia and dysgeusia to the list of screening items for potential infection and recommends that clinicians consider testing and self-isolation of these patients (in the absence of other respiratory diseases such as rhinosinusitis or allergic rhinitis).[220]

## Other diagnostic factors

### fatigue (common)

- Reported in 29% to 69% of patients in case series.[25] [45] [169] [171] [212]
- Patients may also report malaise.

### myalgia (common)

- Reported in 11% to 44% of patients in case series.[25] [26] [45] [169] [170] [212]
- Arthralgia has also been reported.

### anorexia (common)

- Reported in 40% of patients in case series.[45]

### sputum production/expectoration (common)

- Reported in 26% to 33% of patients in case series.[25] [45] [169] [212]

### sore throat (common)

- Reported in 5% to 17% of patients in case series, and usually presents early in the clinical course.[26] [45] [169] [212]
- Children may have pharyngeal erythema.[213]

### gastrointestinal symptoms (uncommon)

- Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea, abdominal pain) have been reported commonly and may be the predominant presenting complaint or the initial symptom. Early case series in China found up to 11% of patients had gastrointestinal symptoms.[25] [26] [45] [169] [171] [212] [221] However, more recent studies report at least one gastrointestinal symptom in up to two-thirds of patients.[42] [222] [223] [224] [225]
- Data from the first 393 hospitalised patients in New York found that 24% of patients presented with diarrhoea, and 19% presented with nausea and vomiting.[211] A case-control study in New York found that 35% of patients had gastrointestinal symptoms, and patients with these symptoms were more likely to have an illness duration of more than 1 week. Gastrointestinal symptoms were associated with a 70% relative increased risk of testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in this study.[226]
- Some patients may present with predominantly gastrointestinal symptoms, especially children.[227] [228] [229]
- Patients may present with nausea or diarrhoea 1 to 2 days prior to onset of fever and breathing difficulties.[45]
- Haematochezia has been reported.[230]

### confusion (uncommon)

- Reported in 9% of patients in case series.[26]

### dizziness (uncommon)

- Reported in 9% to 12% of patients in case series.[45] [171]

### headache (uncommon)

- Reported in 6% to 14% of patients in case series.[25] [26] [45] [169] [171] [212]

### rhinorrhoea or nasal congestion (uncommon)

- Reported in 4% to 5% of patients in case series.[26] [169]
- Nasal congestion has been reported in nearly 4% of patients in one case series.[231]

### haemoptysis (uncommon)

- Reported in 1% to 5% of patients in case series.[25] [169]
- May be a symptom of pulmonary embolism.[232]

### chest pain (uncommon)

- Reported in 2% to 5% of patients in case series.[25] [26]
- May indicate pneumonia.

### conjunctivitis (uncommon)

- Ocular manifestations consistent with conjunctivitis (i.e., conjunctival hyperaemia, chemosis, epiphora, and increased secretions) were reported in 32% of patients in one case series.[233] However, a meta-analysis of over 1100 patients found the overall rate of conjunctivitis to be significantly lower at 1.1%.[234] Conjunctivitis appears to be more frequent in patients with severe illness.[233]

### cutaneous manifestations (uncommon)

- Cutaneous manifestations (e.g., erythematous or maculopapular or morbilliform rash, petechiae, urticaria, vesicles chilblain-like lesions, ischaemic and ecchymotic acral lesions as a manifestation of clotting disorders) have been reported in some patients.[235] [236] [237] [238] [239] [240]
- A UK 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.[241]
- A varicella-like papulovesicular exanthem has been observed rarely in Italy. It typically involves the trunk, has a scattered distribution, and pruritus is mild or absent.[242]
- A case of digitate papulosquamous eruption has been reported, although it is unknown whether it was caused by SARS-CoV-2 infection.[243]
- Cutaneous manIfestations have been reported in children.[244]
- 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.

### 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 |
|---|---|
| **pulse oximetry**<br>• Order in patients with severe illness.<br>• Recommended in patients with respiratory distress and cyanosis.<br>• Clinicians should be aware that patients with COVID-19 can develop 'silent hypoxia': their oxygen saturations can drop to low levels and precipitate acute respiratory failure without the presence of obvious symptoms of respiratory distress. Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognising further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[184] | **may show low oxygen saturation ($SpO_2$ <90%)** |
| **ABG**<br>• Order in patients with severe illness as indicated to detect hypercarbia or acidosis.<br>• Recommended in patients with respiratory distress and cyanosis who have low oxygen saturation ($SpO_2$ <90%). | **may show low partial oxygen pressure** |
| **FBC**<br>• Order in patients with severe illness.<br>• The most common laboratory abnormalities in patients hospitalised with pneumonia include leukopenia, lymphopenia, and leukocytosis. Other abnormalities include neutrophilia, thrombocytopenia, and decreased haemoglobin.[25] [26] [45] [183]<br>• Lymphopenia and thrombocytopenia have been associated with increased risk of severe disease and may be useful as clinical indicators for monitoring disease progression.[245] [246]<br>• High neutrophil-to-lymphocyte ratio is a useful marker for indicating risk for severe illness and poor prognosis.[247] [248] | **leukopenia; lymphopenia; leukocytosis** |
| **coagulation screen**<br>• Order in patients with severe illness.<br>• The most common abnormalities are elevated D-dimer and prolonged prothrombin time.[25] [26] [45]<br>• Non-survivors had significantly higher D-dimer levels and longer prothrombin time and activated partial thromboplastin time compared with survivors in one study.[249] | **elevated D-dimer; prolonged prothrombin time** |
| **comprehensive metabolic panel**<br>• Order in patients with severe illness.<br>• The most common laboratory abnormalities in patients hospitalised with pneumonia include elevated liver transaminases. Other abnormalities include decreased albumin and renal impairment.[25] [26]<br>• Liver function abnormalities may be more common in patients with COVID-19 compared with other types of pneumonia.[201] | **elevated liver transaminases; decreased albumin; renal impairment** |
| **serum procalcitonin**<br>• Order in patients with severe illness. | **may be elevated** |



 

| Test | Result |
|---|---|
| • May be elevated in patients with secondary bacterial infection.[25] [26] May be more common in children.[182] | |
| **serum C-reactive protein**<br>• Order in patients with severe illness.<br>• May be elevated in patients with secondary bacterial infection, or may indicate hyperinflammation.[25] [26]<br>• Increases at the initial stage of disease in patients with severe illness; therefore, it may be useful in identifying patients who might become severely ill.[250] | **may be elevated** |
| **serum ferritin level**<br>• Order in patients with severe illness.<br>• May indicate development of cytokine release syndrome.[251] | **may be elevated** |
| **serum lactate dehydrogenase**<br>• Order in patients with severe illness.<br>• Elevated lactate dehydrogenase has been reported in 73% to 76% of patients.[25] [26] May be more common in patients with COVID-19 compared with other types of pneumonia.[201]<br>• May indicate hyperinflammation. | **may be elevated** |
| **serum creatine kinase**<br>• Order in patients with severe illness.<br>• Elevated creatine kinase has been reported in 13% to 33% of patients.[25] [26]<br>• Indicates muscle or myocardium injury. | **may be elevated** |
| **serum troponin level**<br>• Order in patients with severe illness.<br>• Elevated in patients with cardiac injury.[25] [252]<br>• Other cardiac markers may also be elevated and are associated with severe disease.[253] | **may be elevated** |
| **blood and sputum cultures**<br>• Collect blood and sputum specimens for culture in all patients to rule out other causes of lower respiratory tract infection and sepsis, especially patients with an atypical epidemiological history.[3]<br>• Specimens should be collected prior to starting empirical antimicrobials if possible. | **negative for bacterial infection** |
| **real-time reverse transcription polymerase chain reaction (RT-PCR)**<br>• Molecular testing is required to confirm the diagnosis. Nucleic acid sequencing may be required to confirm the diagnosis.[186] Priorities for testing depend on local guidelines and available resources.<br>• The positive predictive value ranged from 47.3% to 96.4%, and the negative predictive value ranged from 96.8% to 99.9% in one meta-analysis. Pooled sensitivity was 89%.[254]<br>• Collect upper respiratory specimens (nasopharyngeal and oropharyngeal swab or wash) in ambulatory patients and/or lower respiratory specimens (sputum and/or endotracheal aspirate or bronchoalveolar lavage) in patients with more severe respiratory disease. Also consider collecting additional clinical specimens (e.g., blood, stool, urine). Specimens should be collected under appropriate infection prevention and control procedures. Consider the high risk of aerolisation when collecting lower respiratory specimens.[186] | **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 |
|---|---|
| • 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.[186]<br>• Many tests are available under the US Food and Drug Administration's emergency-use authorisation scheme.<br>• A point-of-care test that provides results within hours is available in some countries.[255] While rapid point-of-care tests are available, the World Health Organization does not recommend the use of these tests outside of research settings as they have not been validated as yet.[189]<br>• Tests are available in many laboratories worldwide and testing should be done according to instructions from local health authorities and adhere to appropriate biosafety practices. If testing is not available nationally, specimens should be shipped to an appropriate reference laboratory.<br>• Sensitivity and specificity of RT-PCR for diagnostic testing are unknown.[256]<br>• Collect nasopharyngeal swabs to rule out influenza and other respiratory infections according to local guidance. It is important to note that co-infections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19.[3] [188]<br>• There is emerging evidence that saliva may be a reliable specimen for detecting SARS-CoV-2 by RT-PCR.[257] [258] A test that uses saliva has just been approved.[259]<br>• 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.[260] | |
| **chest x-ray**<br>• Order in all patients with suspected pneumonia.<br>• Unilateral lung infiltrates are found in 25% of patients, and bilateral lung infiltrates are found in 75% of patients.[25] [26] [192] | **unilateral or bilateral lung infiltrates** |
| **computed tomography (CT) chest**<br>• Consider a CT scan of the chest. Consult local guidance on whether to perform a CT scan.<br>• The positive predictive value was low (1.5% to 30.7%) in low-prevalence regions, and the negative predictive value ranged from 95.4% to 99.8% in one meta-analysis. Pooled sensitivity and specificity were 94% and 37%, respectively.[254]<br>• The British Society of Thoracic Imaging (BSTI) recommends CT imaging in patients with clinically suspected COVID-19 who are seriously ill if chest x-ray is uncertain or normal. [BSTI: radiology decision tool for suspected COVID-19] Some institutions in the UK recommend a more pragmatic approach for patients with high clinical suspicion of COVID-19, with chest CT recommended only after two indeterminate or normal chest x-rays in combination with a negative RT-PCR test.[194] 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.[195] | **typical features: multiple bilateral lobular and subsegmental areas of ground-glass opacity or consolidation (usually peripheral or posterior, mainly in the lower lobes, less frequently in right lower lobe), crazy-paving pattern, air bronchograms, reverse halo/perilobular pattern; atypical features: interlobular or septal thickening (smooth or irregular), thickening of the adjacent pleura, subpleural involvement, pleural** |



 

| Test | Result |
| --- | --- |
| • Abnormal chest CT findings have been reported in up to 97% of hospitalised patients.[170] Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[196] CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients.[261] [197] Some patients may present with a normal chest finding despite a positive RT-PCR.[198] 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.[199]<br>• Atypical features appear to be more common in the later stages of disease, or on disease progression.[25] [173] [200]<br>• Older people are more likely to have extensive lung lobe involvement, interstitial changes, and pleural thickening compared with younger patients.[202]<br>• Small nodular ground-glass opacities and consolidation with surrounding halo signs are typical in children.[182] [203] Children tend to have more localised ground-glass opacity, lower ground-glass opacity attenuation, and relatively rare interlobular septal thickening.[204]<br>• Abnormalities can rapidly evolve from focal unilateral to diffuse bilateral ground-glass opacities that progress to, or co-exist with, consolidations within 1 to 3 weeks.[197] The greatest severity of CT findings is usually visible around day 10 after symptom onset, and imaging signs associated with clinical improvement (e.g., resolution of consolidative opacities, reduction in number of lesions and involved lobes) usually occur after week 2 of the disease.[200]<br>• In a cohort of over 1000 patients in a hyperendemic area in China, chest CT had a higher sensitivity for diagnosis of COVID-19 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.[205]<br>[Fig-2] | **effusion, pericardial effusion, bronchiectasis, cavitation, pneumothorax, lymphadenopathy, round cystic changes** |

## Emerging tests

| Test | Result |
|---|---|
| **serology**<br>• 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.[189] Antibody responses to SARS-CoV-2 typically occur during the first 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.[127] [190] Serum samples can be stored to retrospectively define cases when validated serology tests become available. | **positive for SARS-CoV-2 virus antibodies** |
| **lung ultrasound**<br>• There is emerging evidence that lung ultrasound may be a useful aid in the diagnosis of COVID-19 as it has high sensitivity for detecting pleural thickening, subpleural consolidation, and ground-glass opacity. It has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, and repeatability during follow-up. However, it also has limitations (e.g., it is unable to discern chronicity of a lesion) and other imaging modalities may be required.[206] [207] [208] [209] Ultrasound also appears to be a useful imaging modality in children.[210]<br>• [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas] | **B-lines; white lung; pleural line thickening; consolidations with air bronchograms** |



 

# Differential diagnosis

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| **Middle East respiratory syndrome (MERS)** | • Travel history to the Middle East or contact with a confirmed case of MERS.<br>• Differentiating COVID-19 from MERS is not possible from signs and symptoms.<br>• Initial data suggest that the clinical course of COVID-19 is less severe and the case fatality rate is lower compared with MERS. | • Reverse-transcriptase polymerase chain reaction (RT-PCR): positive for MERS-CoV viral RNA. |
| **Severe acute respiratory syndrome (SARS)** | • There have been no cases of SARS reported since 2004. | • RT-PCR: positive for severe acute respiratory syndrome coronavirus (SARS-CoV) viral RNA. |
| **Community-acquired pneumonia** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.<br>• Differentiating COVID-19 from community-acquired bacterial pneumonia is not usually possible from signs and symptoms. However, patients with bacterial pneumonia are more likely to have rapid development of symptoms and purulent sputum. They are less likely to have myalgia, anosmia, or pleuritic pain.[262] [263] | • Blood or sputum culture or molecular testing: positive for causative organism.<br>• RT-PCR: negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA (co-infections are possible).<br>• CT chest: centrilobular nodules, mucoid impactions.[264] |
| **Pneumocystis jirovecii pneumonia** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.<br>• Differentiating COVID-19 from pneumocystis jirovecii pneumonia is not usually possible from signs and symptoms.<br>• Patients are usually immunocompromised (e.g., | • Sputum culture: positive for *Pneumocystis* .<br>• RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).<br>• CT chest: ground-glass opacity is usually more diffusely distributed with a tendency to spare the subpleural regions.[264] |

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| | HIV positive) and duration of symptoms may be longer. | |
| **Influenza infection** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.<br>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.<br>• 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.[265] | • RT-PCR: positive for influenza A or B viral RNA; negative for SARS-CoV-2 viral RNA (co-infections are possible).<br>• CT chest: there is emerging evidence that CT can be used for differentiating between influenza and COVID-19.[266] |
| **Common cold** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.<br>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. | • RT-PCR: positive for causative organism; negative for SARS-CoV-2 viral RNA (co-infections are possible). |
| **Avian influenza A (H7N9) virus infection** | • May be difficult to differentiate based on epidemiological history as avian influenza H7N9 is endemic in China.<br>• Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area when avian influenza is endemic. | • RT-PCR: positive for H7-specific viral RNA. |
| **Avian influenza A (H5N1) virus infection** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset. | • RT-PCR: positive for H5N1 viral RNA. |

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| | • 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. | |
| **Other viral or bacterial respiratory infections** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.<br>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.<br>• Adenovirus and *Mycoplasma* should be considered in clusters of pneumonia patients, especially in closed settings such as military camps and schools. | • Blood or sputum culture of molecular testing: positive for causative organism.<br>• RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible). |
| **Pulmonary tuberculosis** | • Consider diagnosis in endemic areas, especially in patients who are immunocompromised.<br>• History of symptoms is usually longer.<br>• Presence of night sweats and weight loss may help to differentiate. | • Chest x-ray: fibronodular opacities in upper lobes with or without cavitation; atypical pattern includes opacities in middle or lower lobes, or hilar or paratracheal lymphadenopathy, and/or pleural effusion.<br>• Sputum acid-fast bacilli smear and sputum culture: positive.<br>• Molecular testing: positive for *Mycoplasma tuberculosis* . |
| **Febrile neutropenia** | • Suspect neutropenic sepsis in patients with a history of recent systemic anticancer treatment who present with fever (with or without respiratory symptoms) as this can be rapid and life-threatening.[267]<br>• Symptoms of COVID-19 and neutropenic sepsis may be difficult to differentiate at initial presentation. | • CBC: neutropenia.<br>• RT-PCR: negative for SARS-CoV-2 viral RNA. |

# Diagnostic criteria

## World Health Organization: case definitions[111]

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]

## Centers for Disease Control and Prevention: criteria to guide evaluation and laboratory testing for COVID-19[268]

Clinicians should use their judgement to determine whether a patient has signs and symptoms compatible with COVID-19 and whether the patient should be tested. Most patients with confirmed COVID-19 have developed fever and/or symptoms of acute respiratory illness (e.g., cough, difficulty breathing).

Priorities for testing



 

- Priority 1
    - Hospitalised patients
    - Symptomatic healthcare workers
- Priority 2
    - Patients in long-term care facilities with symptoms
    - Patients 65 years of age and older with symptoms
    - Patients with underlying conditions with symptoms
    - First responders with symptoms
- Priority 3
    - Critical infrastructure workers with symptoms
    - Individuals who do not meet any of the above categories with symptoms
    - Healthcare workers and first responders
    - Individuals with mild symptoms in communities experiencing high COVID-19 hospitalisations
- Non-priority
    - Individuals without symptoms

Other considerations that may guide testing are epidemiologic factors such as the occurrence of local community transmission of COVID-19 infections in a jurisdiction. Clinicians are strongly encouraged to test for other causes of respiratory illness, including infections such as influenza.

[CDC: evaluating and testing persons for coronavirus disease 2019 (COVID-19)]

[CDC: priorities for testing patients with suspected COVID-19 infection]

## Infectious Diseases Society of America (IDSA): COVID-19 prioritization of diagnostic testing[269]

IDSA recommends a tiering system for prioritising patients given the current limited availability of near-patient or point-of-care testing. These recommendations will likely change as testing becomes more widely available.

Tier 1

- Critically ill patients in the intensive care unit with unexplained viral pneumonia or respiratory failure, regardless of travel history or close contact with a suspected or confirmed COVID-19 patient.
- Any person, including healthcare workers, with fever or signs/symptoms of a lower respiratory tract illness and close contact with a laboratory-confirmed COVID-19 patient within 14 days of symptom onset (including all residents of a long-term care facility that has a laboratory-confirmed COVID-19 case).
- Any person, including healthcare workers, with fever or signs/symptoms of a lower respiratory tract illness and a history of travel within 14 days of symptom onset to geographical regions where sustained community transmission has been identified.
- Individuals with fever or signs/symptoms of a lower respiratory tract illness who also are immunosuppressed (including patients with HIV), are older, or have underlying chronic health conditions.

- Individuals with fever or signs/symptoms of a lower respiratory tract illness who are critical to pandemic response including healthcare workers, public health officials, and other essential leaders.

Tier 2

- Hospitalised (non-intensive care unit) patients and long-term care facility residents with unexplained fever and signs/symptoms of a lower respiratory tract illness. The number of confirmed COVID-19 cases in the community should be considered.
- As testing becomes more widely available, routine testing of hospitalised patients may be important for infection prevention and management at discharge.

Tier 3

- Patients in outpatient settings who meet the criteria for influenza testing (e.g., older people and/or those with underlying health conditions). Testing in pregnant women and symptomatic children with similar risk factors for complications is encouraged. The number of confirmed COVID-19 cases in the community should be considered.

Tier 4

- Community surveillance as directed by public health and/or infectious diseases authorities.

[IDSA: COVID-19 prioritization of diagnostic testing]

# Step-by-step treatment approach

No specific treatments are known to be effective for COVID-19 yet; therefore, the mainstay of management is early recognition and optimised supportive care to relieve symptoms and to support organ function in more severe illness. Patients should be managed in a hospital setting where possible; however, home care may be suitable for selected patients with mild illness unless there is concern about rapid deterioration or an inability to promptly return to hospital if necessary. Children are less likely to require hospitalisation, but if admitted, generally only require supportive care.[12] [17]

[BMJ talk medicine podcast: coping with Covid-19 - advice from a New York City intensivist]

Rationing of medical resources may be required during the pandemic if healthcare infrastructures are overwhelmed. This raises many ethical questions on how to best triage patients to save the most lives. Recommendations have been suggested, but there is no clear international guidance on this issue as yet.[274] [275] [276] [277] [278]

## Infection prevention and control

Immediately isolate all suspected or confirmed cases in an area separate from other patients. Suspected cases should be given a mask and kept at least 1 metre (3 feet) from other suspected cases. It is important to note that recommended distances differ between countries and you should consult local guidance. Implement appropriate infection prevention and control procedures. COVID-19 is a notifiable disease; report all suspected and confirmed cases to your local health authorities.

[BMJ: covid-19 - PPE guidance]

Detailed guidance on infection prevention and control procedures are available from the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC):

- [WHO: infection prevention and control during health care when COVID-19 is suspected]
- [CDC: interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings]
- [CDC: strategies to optimize the supply of PPE and equipment]

The WHO recommends that patients should remain in isolation for 2 weeks after symptoms disappear, and visitors should not be allowed until the end of this period.[279] Guidance on when to stop isolation depends on local circumstances and may differ between countries; consult local guidelines.

## Severe COVID-19: location of care and admission

Promptly admit patients with pneumonia or acute respiratory distress to an appropriate healthcare facility and start supportive care depending on the clinical presentation. Patients with impending or established respiratory failure should be admitted to an intensive care unit. Approximately 14% of patients in China presented with severe illness requiring oxygen therapy, and 5% presented with critical illness requiring intensive care unit treatment.[7] However, data from New York found that 14% of hospitalised patients required admission to the intensive care unit, and 12% required mechanical ventilation.[115] The most common reasons for intensive care unit admission are hypoxaemic respiratory failure leading to mechanical ventilation and hypotension.[280] The median time from onset of symptoms to hospital admission is reported to be approximately 7 days.[25] [45] Hospitalisation rates increase with age, and are highest among older adults or patients with underlying conditions.[281]

Treatment and care planning

- 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.[282]

Admission to critical care

- 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 ≥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.[283]

## Severe COVID-19: supportive care

Oxygen

- Give supplemental oxygen at a rate of 5 L/minute to patients with severe acute respiratory infection and respiratory distress, hypoxaemia, shock, or $SpO_2$ <90%.[3] [284] Titrate flow rates to reach a target $SpO_2$ ≥94% during resuscitation.[3] Use a face mask with a reservoir bag (at 10-15 L/minute) if the patient is in critical condition.
- Once the patient is stable, the target $SpO_2$ is >90% in children and non-pregnant adults, and ≥92% to 95% in pregnant women. Nasal prongs or a nasal cannula are preferred in young children.[3] Some guidelines recommend that $SpO_2$ should be maintained no higher than 96%.[284]
- Some locations may recommend different targets in order to support prioritisation of oxygen flow for the most severely ill patients in hospital. For example, NHS England recommends a target of 92% to 95% (or 90% to 94% if clinically appropriate).[285]
- Oxygen delivery in patients with severe hypoxaemia can be increased by using a non-rebreathing mask and prone positioning.[286]
- Early self-proning of awake, non-intubated patients improved oxygen saturation in a small pilot study of 50 patients in a New York emergency department.[287]

Intravenous fluids

- Manage fluids conservatively in adults and children with severe acute respiratory infection when there is no evidence of shock as aggressive fluid resuscitation may worsen oxygenation.[3]

Antimicrobials



 

- Start empirical antimicrobials to cover other potential bacterial pathogens that may cause respiratory infection according to local protocols. Give within 1 hour of initial patient assessment for patients with suspected sepsis. Choice of empirical antimicrobials should be based on the clinical diagnosis, and local epidemiology and susceptibility data. Consider treatment with a neuraminidase inhibitor until influenza is ruled out. De-escalate empirical therapy based on microbiology results and clinical judgement.[3] There is insufficient evidence to recommend empirical broad-spectrum antimicrobials in the absence of another indication. Reassess antimicrobial use daily in order to minimise the consequences of unnecessary antimicrobial therapy.[288]
- Some patients with severe illness may require continued antimicrobial therapy once COVID-19 has been confirmed depending on the clinical circumstances.

Monitoring

- Monitor patients closely for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and immediately start general supportive care interventions as indicated (e.g., haemodialysis, vasopressor therapy, fluid resuscitation, ventilation, antimicrobials) as appropriate.[3]

Prevention of complications

- Implement standard interventions to prevent complications associated with critical illness.[3] Complications such as acute respiratory distress syndrome (ARDS), sepsis, and septic shock should be managed according to usual protocols. See our Complications section for more information.

Palliative care

- Follow local palliative care guidelines for patients in the last days and hours of life.

## Severe COVID-19: symptom management

Managing fever

- Guidelines recommend an antipyretic for the relief of fever.[3] [284] However, current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections.[289] If used, these drugs should only be taken when necessary while symptoms are present.
- Some clinicians have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen could worsen COVID-19 or have a negative impact on disease outcome based on anecdotal reports and the fact these drugs can mask symptoms of bacterial infections.[290] [291] There is currently no strong evidence to support this. The European Medicines Agency, the US Food and Drug Administration, and the Commission of Human Medicines do not recommend avoiding NSAIDs in COVID-19 when clinically indicated.[292] [293] [294] [295] The WHO has confirmed that there is no evidence at present of severe adverse events in COVID-19 patients taking NSAIDs, or 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.[296] The National Institute for Health and Care Excellence in the UK has updated its guidance to recommend either paracetamol or ibuprofen for the treatment of fever; however, it recommends taking the lowest effective dose of ibuprofen for the shortest period needed to control symptoms.[282] [297]

Managing cough

- Advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients aged 1 year and older). Consider short-term use of an oral opioid in adults if the cough is distressing to the patient.[282]

Managing 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.[282]

Managing anxiety, delirium, and agitation

- Identify and treat any reversible causes (e.g., offer reassurance, treat hypoxia). Consider a benzodiazepine for the management of anxiety or agitation. Consider haloperidol or a phenothiazine for the management of delirium.[282]

## Severe COVID-19: high flow nasal oxygen/non-invasive ventilation

Provide advanced oxygen or non-invasive ventilation in patients who are deteriorating and failing to respond to standard oxygen therapy.[3] Follow local infection prevention and control procedures to prevent transmission to healthcare workers, especially when performing aerosol-generating procedures. Novel methods to protect clinicians without access to standard personal protective equipment during aerosol-generating procedures have been suggested (e.g., aerosol box, plastic drapes, helmet devices, plastic negative pressure canopy).[298] [299] [300] [301]

Consider a trial of high-flow nasal oxygen or non-invasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in patients with hypoxaemic respiratory failure.[3] [284] These procedures may avoid the need for intubation and mechanical ventilation; however, they have a higher risk of aerosol generation.[302]

There is ongoing debate about the optimal mode of respiratory support before mechanical ventilation, and you should check local guidelines for preferred options.[303] NHS England recommends CPAP as the preferred form of non-invasive ventilation, and doesn't advocate the use of high-flow nasal oxygen based on a lack of efficacy, oxygen use, and infection spread. High-flow oxygen delivery can place a strain on oxygen supplies with the risk of site supply failure. Early CPAP may provide a bridge to invasive mechanical ventilation. Use of BiPAP should be reserved for patients with hypercapnic acute or chronic ventilatory failure.[304] The US National Institutes of Health (NIH) recommends high-flow nasal oxygen for acute hypoxaemic respiratory failure over non-invasive positive pressure ventilation, unless high-flow nasal oxygen is not available.[288] Despite the trend to avoid high-flow nasal oxygen, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[305]

Monitor patients closely for clinical deterioration that could result in the need for urgent intubation.[3] Patients with lower $PaO_2$/fraction of inspired oxygen ($FiO_2$) were more likely to experience failure with high-flow nasal oxygen and require ventilation in one study.[306]

## Severe COVID-19: mechanical ventilation

Consider intubation and mechanical ventilation in patients who are acutely deteriorating despite advanced oxygen/non-invasive ventilatory support measures, especially those with fatigue and at risk for exhaustion because of respiratory distress. Two-thirds of patients who required critical care in the UK had mechanical



 

ventilation within 24 hours of admission.[307] 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.[211]

Endotracheal intubation should be performed by an experienced provider using airborne precautions. Intubation by video laryngoscopy is recommended if possible.[288] Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require pre-oxygenation with 100% $FiO_2$ for 5 minutes.[3]

The WHO, National Institutes of Health, and Surviving Sepsis Campaign guidelines recommend that 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.[3] [284] [288]

Although some patients with COVID-19 pneumonia can meet the criteria for ARDS, there is some emerging evidence that COVID-19 pneumonia may be its own specific disease with atypical phenotypes. Anecdotal evidence from Italy and the US suggests that the main characteristic of the atypical presentation is the dissociation between well-preserved lung mechanics and the severity of hypoxaemia.[287] [308] [309] Italian clinicians have defined the two disease phenotypes for COVID-19 pneumonia as follows:

- Type L (or non-ARDS, type 1) – severe hypoxaemia associated with: low elastance; low ventilation-to-perfusion ratio; low lung weight; low lung recruitability (the near normal compliance may explain why some patients present without dyspnoea)
- Type H (or ARDS, type 2) – severe hypoxaemia associated with: high elastance; high right-to-left shunt; high lung weight; high lung recruitability.

These patients are clearly distinguishable by CT scan. Patients may initially present with the type L phenotype, which may remain unchanged for a period of time and then either improve or worsen, or it may transition to type H. Type H pattern fits the severe acute respiratory distress syndrome criteria, and only 20% to 30% of patients in the case series of 150 patients displayed this phenotype. Type L appeared to be more common (more than 50% of patients) in this series.[309] [310] [311] Other phenotypes have also been proposed.[312]

Italian 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.[308] High PEEP may have a detrimental effect on patients with normal compliance, and a lower PEEP strategy should be considered in patients with the type L/type 1 phenotype. NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[313] PEEP should be carefully titrated.[286] You should consult an intensivist with experience in treating COVID-19 patients for more detailed guidance on this rapidly evolving and controversial issue.

Consider prone ventilation for 12 to 16 hours per day in patients with persistent severe hypoxic failure.[3] [284] [288] [314] Prone position may be less useful in patients with the type L/type 1 phenotype.[309] Pregnant women may benefit from being placed in the lateral decubitus position.[3] A small cohort study of 12 patients in Wuhan City, China, with COVID-19-related acute respiratory distress syndrome suggests that spending periods of time in the prone position may improve lung recruitability.[315]

A trial of an inhaled pulmonary vasodilator may be considered in adults who have severe acute respiratory distress syndrome and hypoxaemia despite optimising ventilation. However, this should be tapered off if

there is no rapid improvement in oxygenation. Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[284] [288]

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.[316]

## Severe COVID-19: extracorporeal membrane oxygenation

There is insufficient evidence to recommend either for or against the routine use of extracorporeal membrane oxygenation (ECMO).[288] Some patients may require ECMO according to availability and expertise if the above methods fail.[3] [284] [314] [317] However, ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[318] 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.[319] [320]

## Severe COVID-19: experimental therapies

Corticosteroids

- Corticosteroids are being used in some patients with COVID-19; however, they have been found to be ineffective and are not recommended.[25] [321] [322] A meta-analysis of over 5000 patients found that corticosteroid treatment in patients with COVID-19 was associated with longer hospital stays and a higher rate of mortality.[323]
- The WHO (as well as other international pneumonia guidelines) does not routinely recommend systemic corticosteroids for the treatment of viral pneumonia or acute respiratory distress syndrome unless they are indicated for another reason.[3]
- The Infectious Diseases Society of America recommends against the use of corticosteroids in patients with COVID-19, except in the context of a clinical trial.[324]
- Surviving Sepsis Campaign guidelines on the treatment of critically ill patients with COVID-19 suggest that adults with acute respiratory distress syndrome who are receiving mechanical ventilation should receive corticosteroids, although this recommendation is based on weak evidence.[284] NIH guidelines say that there is insufficient evidence to recommend for or against the use of systemic corticosteroids in mechanically ventilated patients with acute respiratory distress syndrome.[288]

Other experimental therapies

- Drug therapies (e.g., antivirals) are being used in patients with COVID-19; however, unlicensed or experimental treatments should only be administered in the context of ethically-approved clinical trials.[3] See our Emerging section for more information about these treatments.

## Mild COVID-19 with risk factors or moderate COVID-19

Patients with mild illness who have risk factors for poor outcomes (i.e., age >60 years, presence of comorbidities) should also be prioritised for hospital admission.[270] Patients with moderate illness (e.g., dyspnoea but blood oxygen saturation is at least 94%) are also usually hospitalised.[325] These patients should be managed in the same way as severe COVID-19 (above) depending on the clinical presentation.



 

## Mild COVID-19 without risk factors

All laboratory-confirmed cases, regardless of severity, should be managed in a healthcare facility where possible. In situations where this is not possible, patients with mild illness and no risk factors (i.e., age >60 years, presence of comorbidities) can be isolated in non-traditional facilities (e.g., repurposed hotels or stadiums) or at home. This will depend on guidance from local health authorities and available resources. Forced quarantine orders are being used in some countries.[270]

Home care can be considered when the patient can be cared for by family members and follow-up with a healthcare provider or public health personnel is possible. The decision requires careful clinical judgement and should be informed by an assessment of the patient's home environment.[270]

Patients and household members should follow appropriate infection prevention and control measures while the patient is in home care. Detailed guidance is available from the WHO and CDC:

- [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)]

Recommend symptomatic therapies (as per the recommendations above) and advise patients to keep hydrated but not to take too much fluid as this can worsen oxygenation. Advise patients to improve air circulation by opening a window or door (fans can spread infection and should not be used).[282]

Monitor patients closely and advise them to seek medical care if symptoms worsen as mild illness can rapidly progress to lower respiratory tract disease. Two negative test results (on samples collected at least 24 hours apart) are required before the patient can be released from home isolation. If testing is not possible, the patient should remain in isolation for an additional 2 weeks after symptoms resolve.[270] Guidance on when to stop isolation depends on local circumstances and may differ between countries; consult local guidelines.

## Pregnancy and breastfeeding

Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as mental health and psychosocial support. There is no evidence to suggest that pregnant women are more likely to contract COVID-19, or present with increased risk of severe illness or fetal compromise. Data on pregnant women with COVID-19 are limited; however, pregnant women can generally be treated with the same supportive therapies detailed above, taking into account the physiological changes that occur with pregnancy.[3] [326]

Location of care

- Manage suspected and confirmed cases in a hospital setting with appropriate maternal and fetal monitoring whenever possible. Women with severe illness or complications may require admission to an intensive care unit. 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.[191] [327] [328]
- 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)]

Delivery

- Choice of delivery and timing should be individualised based on gestational age, as well as maternal, fetal, and delivery conditions. Induction of labour and vaginal delivery is preferred in pregnant women with confirmed COVID-19 infection to avoid unnecessary surgical complications; however, an emergency caesarean delivery may be required if medically justified (e.g., in patients with complications such as sepsis or if there is fetal distress). A negative pressure isolation room is recommended in confirmed cases for labour, delivery, and neonatal care, if possible.[3] [191] [328]
- Corticosteroid therapy may be considered in women who are at risk of preterm birth from 24 to 37 weeks' gestation for fetal lung maturation, but caution is advised as this could potentially worsen the maternal clinical condition, and the decision should be made in conjunction with the multidisciplinary team.[3] [191] [328] [329]

Newborns and breastfeeding

- Babies born to mothers with suspected or confirmed infection should be considered a person under investigation and tested at 24 hours and 48 hours after birth.[330]
- The WHO recommends that mothers and infants should remain together when possible, and 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).[3] The CDC recommends that temporary separation of the mother and baby should be considered on a case-by-case basis using shared-decision making between the mother and the clinical team, at least until the mother's transmission-based precautions are discontinued. It recommends that mothers who intend to breastfeed should be encouraged to express their breast milk using a dedicated breast pump and using appropriate infection prevention and control measures in order to maintain milk supply. Expressed milk should be fed to the newborn by a healthy carer.[331] Separation appears to be the best option for mothers who are severely or critically ill.[191] Consult local guidelines for specific recommendations.
- After discharge, advise mothers with COVID-19 to practice prevention measures (e.g., distance, hand hygiene, respiratory hygiene/mask) for newborn care until they are afebrile for 72 hours without use of antipyretics and at least 7 days have passed since symptoms first appeared. A newborn with documented infection requires close outpatient follow-up after discharge.[330] Advise mothers with suspected or confirmed COVID-19 to take all possible precautions when breastfeeding, including hand hygiene and wearing a cloth face covering.[332]

# 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



 

| Initial ( summary ) | | |
|---|---|---|
| **suspected COVID-19** | | |
| | **1st** | **isolation and infection prevention and control procedures** |
| | **plus** | **empirical antimicrobials** |
| | **plus** | **monitoring** |
| | **adjunct** | **supportive care** |
| | **adjunct** | **antipyretic** |
| | **adjunct** | **antitussive** |

## Acute ( summary )

**confirmed COVID-19**

| | | |
|---|---|---|
| **moderate to severe illness; mild illness with risk factors** | **1st** | **hospital admission** |
| | **plus** | **infection prevention and control procedures** |
| | **plus** | **treatment and care planning** |
| | **plus** | **monitoring** |
| | **adjunct** | **supportive care** |
| | **adjunct** | **empirical antimicrobials** |
| | **adjunct** | **antipyretic** |
| | **adjunct** | **antitussive** |
| | **adjunct** | **high-flow nasal oxygen or non-invasive ventilation** |
| | **adjunct** | **invasive mechanical ventilation** |
| | **adjunct** | **prone positioning** |
| | **adjunct** | **inhaled pulmonary vasodilator** |
| | **adjunct** | **extracorporeal membrane oxygenation** |
| | **adjunct** | **experimental therapies** |
| **mild illness with no risk factors** | **1st** | **isolation in non-traditional facility or at home** |
| | **plus** | **monitoring** |
| | **plus** | **supportive care** |
| | **adjunct** | **antipyretic** |
| | **adjunct** | **antitussive** |

# 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

# Initial

**suspected COVID-19**

**1st** **isolation and infection prevention and control procedures**

» Immediately isolate all suspected cases in an area separate from other patients, and implement appropriate infection prevention and control procedures. Suspected cases should be given a mask and kept at least 1 metre (3 feet) from other suspected cases. It is important to note that recommended distances differ between countries and you should consult local guidance.

» [BMJ: covid-19 - PPE guidance]

» Detailed guidance is available from the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC):

» [WHO: infection prevention and control during health care when COVID-19 is suspected]

» [CDC: interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings]

» COVID-19 is a notifiable disease; report all suspected cases to your local health authorities.

» Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as mental health and psychosocial support.[3] [328]

**plus** **empirical antimicrobials**

Treatment recommended for ALL patients in selected patient group

» Start empirical antimicrobials to cover other potential bacterial pathogens that may cause respiratory infection according to local protocols. Give within 1 hour of initial patient assessment for patients with suspected sepsis. Choice of empirical antimicrobials should be based on the clinical diagnosis, and local epidemiology and susceptibility data.[3] There is insufficient evidence to recommend empirical broad-spectrum antimicrobials in the absence of another indication. Reassess antimicrobial use daily in order to minimise the consequences of unnecessary antimicrobial therapy.[288]

» Consider treatment with a neuraminidase inhibitor until influenza is ruled out.[3]



 

## Initial

» De-escalate empirical therapy based on microbiology results and clinical judgement.

**plus** **monitoring**

Treatment recommended for ALL patients in selected patient group

» Monitor patients closely for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and immediately start general supportive care interventions as indicated (e.g., haemodialysis, vasopressor therapy, fluid resuscitation, ventilation, antimicrobials) as appropriate.[3]

**adjunct** **supportive care**

Treatment recommended for SOME patients in selected patient group

» Immediately start supportive care based on the clinical presentation if necessary.

» Oxygen: give supplemental oxygen at a rate of 5 L/minute to patients with severe acute respiratory infection and respiratory distress, hypoxaemia, shock, or $SpO_2$ <90%.[3] [284] Titrate flow rates to reach a target $SpO_2$ ≥94% during resuscitation. Use a face mask with a reservoir bag (at 10-15 L/minute) if the patient is in critical condition. Once the patient is stable, the target $SpO_2$ is >90% in children and non-pregnant adults, and ≥92% to 95% in pregnant women. Nasal prongs or a nasal cannula are preferred in young children.[3] Some guidelines recommend that $SpO_2$ should be maintained no higher than 96%.[284] Some locations may recommend different targets in order to support prioritisation of oxygen flow for the most severely ill patients in hospital. For example, NHS England recommends a target of 92% to 95% in adults in the first instance (or 90% to 94% if clinically appropriate).[285] Oxygen delivery in patients with severe hypoxaemia can be increased by using a non-rebreathing mask and prone positioning.[286]

» Intravenous fluids: manage fluids conservatively in adults and children with severe acute respiratory infection when there is no evidence of shock as aggressive fluid resuscitation may worsen oxygenation.[3]

**adjunct** **antipyretic**

Treatment recommended for SOME patients in selected patient group

### Primary options

## Initial

» 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

» Guidelines recommend an antipyretic for the relief of fever.[3] [284] However, current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections.[289] If used, these drugs should only be taken when necessary while symptoms are present.

» Some clinicians have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen could worsen COVID-19 or have a negative impact on disease outcome based on anecdotal reports and the fact these drugs can mask symptoms of bacterial infections.[290] [291] There is currently no strong evidence to support this. The European Medicines Agency, the Food and Drug Administration, and the Commission of Human Medicines do not recommend avoiding NSAIDs in COVID-19 when clinically indicated.[292] [293] [294] [295] The WHO has confirmed that there is no evidence at present of severe adverse events in COVID-19 patients taking NSAIDs, or 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.[296] The National Institute for Health and Care Excellence in the UK has updated its guidance to recommend either paracetamol or ibuprofen for the treatment of fever; however, it recommends taking the lowest effective dose of ibuprofen for the shortest period needed to control symptoms.[282] [297]

» Ibuprofen is not recommended in pregnant women (especially in the third trimester) or children <3 months of age (age cut-offs vary by country).

**adjunct** **antitussive**

Treatment recommended for SOME patients in selected patient group

### Primary options

 

## Initial

» codeine phosphate: 15-30 mg orally every 4 hours when required initially (up to 4 doses/day), increase to 30-60 mg every 6 hours when required if necessary, maximum 240 mg/day

### Secondary options

» morphine sulfate: adults: 2.5 to 5 mg orally every 4 hours when required initially, increase to 5-10 mg every 4 hours when required if necessary

» Advise patients to avoid lying on their back as this makes coughing ineffective.

» Use simple measures first (e.g., a teaspoon of honey in patients aged 1 year and older).

» Consider short-term use of an oral opioid in adults if the cough is distressing to the patient. Codeine (linctus or tablet) is the preferred first-line option, with oral morphine solution reserved as a second-line option.[282]

# Acute

## confirmed COVID-19

### moderate to severe illness; mild illness with risk factors

**1st** **hospital admission**

» Promptly admit patients with pneumonia or acute respiratory distress to an appropriate healthcare facility. Patients with impending or established respiratory failure should be admitted to an intensive care unit.[3]

» Patients with mild illness who have risk factors for poor outcomes (i.e., age >60 years, presence of comorbidities) should also be prioritised for hospital admission when possible.[270] Patients with moderate illness (e.g., dyspnoea but blood oxygen saturation is at least 94%) are also usually hospitalised.[325] Further management of these patients depends on the clinical presentation and not all of the treatments below will apply to these patients.

» Manage suspected and confirmed cases in pregnant women in a hospital setting with appropriate maternal and fetal monitoring whenever possible. Women with severe illness or complications may require admission to an intensive care unit.[191] [327] [328] Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as mental health and psychosocial support.[3] [328]

**plus** **infection prevention and control procedures**

Treatment recommended for ALL patients in selected patient group

» Immediately isolate all confirmed cases in an area separate from other patients, and implement appropriate infection prevention and control procedures.

» [BMJ: covid-19 - PPE guidance]

» Detailed guidance is available from the WHO and the CDC:

» [WHO: infection prevention and control during health care when COVID-19 is suspected]

» [CDC: interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings]



 

## Acute

» COVID-19 is a notifiable disease; report all confirmed cases to your local health authorities.

» The WHO recommends that patients should remain in isolation for 2 weeks after symptoms disappear, and visitors should not be allowed until the end of this period.[279] Guidance on when to stop isolation depends on local circumstances and may differ between countries; consult local guidelines.

**plus** **treatment and care planning**

Treatment recommended for ALL patients in selected patient group

» Assess all adults for frailty on admission to hospital, irrespective of age and COVID-19 status, using the Clinical Frailty Scale.[283] [Clinical frailty scale]

» 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.[282]

» Involve critical care teams in discussions about admission to critical care.[283]

**plus** **monitoring**

Treatment recommended for ALL patients in selected patient group

» Monitor patients closely for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and immediately start general supportive care interventions as indicated (e.g., haemodialysis, vasopressor therapy, fluid resuscitation, ventilation, antimicrobials) as appropriate.[3]

**adjunct** **supportive care**

Treatment recommended for SOME patients in selected patient group

» Immediately start supportive care, if necessary.

» Oxygen: give supplemental oxygen at a rate of 5 L/minute to patients with severe acute respiratory infection and respiratory distress, hypoxaemia, shock, or $SpO_2$ <90%.[3] [284] Titrate flow rates to reach a target $SpO_2$ ≥94%

## Acute

during resuscitation. Use a face mask with a reservoir bag (at 10-15 L/minute) if the patient is in critical condition. Once the patient is stable, the target $SpO_2$ is >90% in children and non-pregnant adults, and ≥92% to 95% in pregnant women. Nasal prongs or a nasal cannula are preferred in young children.[3] Some guidelines recommend that $SpO_2$ should be maintained no higher than 96%.[284] Some locations may recommend different targets in order to support prioritisation of oxygen flow for the most severely ill patients in hospital. For example, NHS England recommends a target of 92% to 95% in adults in the first instance (or 90% to 94% if clinically appropriate).[285] Oxygen delivery in patients with severe hypoxaemia can be increased by using a non-rebreathing mask and prone positioning.[286]

» Intravenous fluids: manage fluids conservatively in adults and children with severe acute respiratory infection when there is no evidence of shock as aggressive fluid resuscitation may worsen oxygenation.[3]

» Managing 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.[282]

» Managing anxiety, delirium, and agitation: identify and treat any reversible causes (e.g., offer reassurance, treat hypoxia). Consider a benzodiazepine for the management of anxiety or agitation. Consider haloperidol or a phenothiazine for the management of delirium.[282]

» Implement standard interventions to prevent complications associated with critical illness.[3]

**adjunct** **empirical antimicrobials**

Treatment recommended for SOME patients in selected patient group

» Patients with severe illness may require continued antimicrobial therapy once COVID-19 has been confirmed depending on the clinical circumstances.

**adjunct** **antipyretic**

Treatment recommended for SOME patients in selected patient group



 

# Acute

### 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

» Guidelines recommend an antipyretic for the relief of fever.[3] [284] However, current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections.[289] If used, these drugs should be taken only when necessary while symptoms are present.

» Some clinicians have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen could worsen COVID-19 or have a negative impact on disease outcome based on anecdotal reports and the fact these drugs can mask symptoms of bacterial infections.[290] [291] There is currently no strong evidence to support this. The European Medicines Agency, the Food and Drug Administration, and the Commission of Human Medicines do not recommend avoiding NSAIDs in COVID-19 when clinically indicated.[292] [293] [294] [295] The WHO has confirmed that there is no evidence at present of severe adverse events in COVID-19 patients taking NSAIDs, or 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.[296] The National Institute for Health and Care Excellence in the UK has updated its guidance to recommend either paracetamol or ibuprofen for the treatment of fever; however, it recommends taking the lowest effective dose of ibuprofen for the shortest period needed to control symptoms.[282] [297]

» Ibuprofen is not recommended in pregnant women (especially in the third trimester) or children <3 months of age (age cut-offs vary by country).

**adjunct** **antitussive**

Treatment recommended for SOME patients in selected patient group

# Acute

### Primary options

» codeine phosphate: 15-30 mg orally every 4 hours when required initially (up to 4 doses/day), increase to 30-60 mg every 6 hours when required if necessary, maximum 240 mg/day

### Secondary options

» morphine sulfate: adults: 2.5 to 5 mg orally every 4 hours when required initially, increase to 5-10 mg every 4 hours when required if necessary

» Advise patients to avoid lying on their back as this makes coughing ineffective.

» Use simple measures first (e.g., a teaspoon of honey in patients aged 1 year and older).

» Consider short-term use of an oral opioid in adults if the cough is distressing to the patient. Codeine (linctus or tablet) is the preferred first-line option, with oral morphine solution reserved as a second-line option.[282]

**adjunct** **high-flow nasal oxygen or non-invasive ventilation**

Treatment recommended for SOME patients in selected patient group

» Provide advanced oxygen/non-invasive ventilatory support in patients who are deteriorating and failing to respond to standard oxygen therapy, especially those with fatigue and at risk for exhaustion because of respiratory distress.[3]

» These procedures may avoid the need for intubation and mechanical ventilation; however, they have a higher risk of aerosol generation.[302] Follow local infection prevention and control procedures to prevent transmission to healthcare workers, especially when performing aerosol-generating procedures.

» Consider a trial of high-flow nasal oxygen or non-invasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in patients with hypoxaemic respiratory failure.[3] [284]

» There is ongoing debate about the optimal mode of respiratory support before mechanical ventilation, and you should check local guidelines for preferred options.[303] NHS England recommends CPAP as the preferred



 

## Acute

form of non-invasive ventilation, and doesn't advocate the use of high-flow nasal oxygen based on a lack of efficacy, oxygen use, and infection spread. High-flow oxygen delivery can place a strain on oxygen supplies with the risk of site supply failure. Early CPAP may provide a bridge to invasive mechanical ventilation. Use of BiPAP should be reserved for patients with hypercapnic acute or chronic ventilatory failure.[304] The US National Institutes of Health recommends high-flow nasal oxygen for acute hypoxaemic respiratory failure over non-invasive positive pressure ventilation, unless high-flow nasal oxygen is not available.[288]

» Despite the trend to avoid high-flow nasal oxygen, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[305]

» Monitor patients closely for clinical deterioration that could result in the need for urgent intubation.[3] Patients with lower $PaO_2$/fraction of inspired oxygen ($FiO_2$) were more likely to experience failure with high-flow nasal oxygen and require ventilation in one study.[306]

**adjunct** **invasive mechanical ventilation**

Treatment recommended for SOME patients in selected patient group

» Consider intubation and mechanical ventilation in patients who are acutely deteriorating.[3]

» Endotracheal intubation should be performed by an experienced provider using airborne precautions. Intubation by video laryngoscopy is recommended if possible.[288]

» Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require pre-oxygenation with 100% $FiO_2$ for 5 minutes.[3]

» The WHO, National Institutes of Health, and Surviving Sepsis Campaign guidelines recommend that 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.[3] [284] [288]

» However, Italian 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

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findings rather than using standard protocols. They note that many COVID-19 patients have an atypical presentation, showing a dissociation between well-preserved lung mechanics and the severity of hypoxaemia.[287] [308] [309] [310] [311] High PEEP may have a detrimental effect on patients with normal compliance, and a lower PEEP strategy should be considered in these patients. NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[313] PEEP should be carefully titrated.[286]

» You should consult an intensivist with experience in treating COVID-19 patients for more detailed guidance on this rapidly evolving and controversial issue.

» Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[284] [288]

**adjunct** **prone positioning**

Treatment recommended for SOME patients in selected patient group

» Consider prone ventilation for 12 to 16 hours per day in patients with persistent severe hypoxic failure.[3] [284] [288] [314]

» Pregnant women may benefit from being placed in the lateral decubitus position.[3]

» A small cohort study of 12 patients in Wuhan, China, with COVID-19-related acute respiratory distress syndrome suggests that spending periods of time in the prone position may improve lung recruitability.[315]

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

Treatment recommended for SOME patients in selected patient group

» A trial of an inhaled pulmonary vasodilator may be considered in adults who have severe acute respiratory distress syndrome and hypoxaemia despite optimising ventilation. However, this should be tapered off if there is no rapid improvement in oxygenation.[284] [288]

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

Treatment recommended for SOME patients in selected patient group

» Some patients may require extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[3] [284] [314] However, ECMO is not

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suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[318]

» There is insufficient evidence to recommend either for or against the routine use of ECMO.[288] 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.[319] [320]

**adjunct** **experimental therapies**

Treatment recommended for SOME patients in selected patient group

» Consider using experimental drug therapies. Antivirals and other drugs are being used in patients with COVID-19; however, unlicensed or experimental treatments should only be administered in the context of ethically-approved clinical trials.[3] See the Emerging section for more information about these treatments.

**mild illness with no risk factors** **1st** **isolation in non-traditional facility or at home**

» Patients with mild illness and no risk factors (i.e., age >60 years, presence of comorbidities) can be isolated in non-traditional facilities (e.g., repurposed hotels or stadiums) or at home when management in a healthcare facility is not possible. This will depend on guidance from local health authorities and available resources.[270] Forced quarantine orders are being used in some countries.

» Home care can be considered when the patient can be cared for by family members and follow-up with a healthcare provider or public health personnel is possible. The decision requires careful clinical judgement and should be informed by an assessment of the patient's home environment.[270]

» Consider home care in pregnant 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.[191] [327] [328]

» Patients and household members should follow appropriate infection prevention and control measures. Detailed guidance is available from the WHO and the CDC:

## Acute

» [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)]

» Two negative test results (on samples collected at least 24 hours apart) are required before the patient can be released from home isolation. If testing is not possible, the patient should remain in isolation for an additional 2 weeks after symptoms resolve.[270] Guidance on when to stop isolation depends on local circumstances and may differ between countries; consult local guidelines.

**plus** **monitoring**

Treatment recommended for ALL patients in selected patient group

» Monitor patients closely and advise them to seek medical care if symptoms worsen as mild illness can rapidly progress to lower respiratory tract disease.

» Ultrasound fetal surveillance is recommended every 2 weeks in pregnant women.[328]

**plus** **supportive care**

Treatment recommended for ALL patients in selected patient group

» Advise patients to keep hydrated but not to take too much fluid as this can worsen oxygenation.[270]

» Advise patients to improve air circulation by opening a window or door (fans can spread infection and should not be used).[282]

**adjunct** **antipyretic**

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
» 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



 

## Acute

» Guidelines recommend an antipyretic for the relief of fever.[3] However, current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections.[289] If used, these drugs should only be taken when necessary while symptoms are present.

» Some clinicians have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen could worsen COVID-19 or have a negative impact on disease outcome based on anecdotal reports and the fact these drugs can mask symptoms of bacterial infections.[290] [291] There is currently no strong evidence to support this. The European Medicines Agency, the Food and Drug Administration, and the Commission of Human Medicines do not recommend avoiding NSAIDs in COVID-19 when clinically indicated.[292] [293] [294] [295] The WHO has confirmed that there is no evidence at present of severe adverse events in COVID-19 patients taking NSAIDs, or 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.[296] The National Institute for Health and Care Excellence in the UK has updated its guidance to recommend either paracetamol or ibuprofen for the treatment of fever; however, it recommends taking the lowest effective dose of ibuprofen for the shortest period needed to control symptoms.[282] [297]

» Ibuprofen is not recommended in pregnant women (especially in the third trimester) or children <3 months of age (age cut-offs vary by country).

**adjunct** **antitussive**

Treatment recommended for SOME patients in selected patient group

### Primary options

» codeine phosphate: 15-30 mg orally every 4 hours when required initially (up to 4 doses/day), increase to 30-60 mg every 6 hours when required if necessary, maximum 240 mg/day

### Secondary options

» morphine sulfate: adults: 2.5 to 5 mg orally every 4 hours when required initially, increase to 5-10 mg every 4 hours when required if necessary

## Acute

» Advise patients to avoid lying on their back as this makes coughing ineffective.

» Use simple measures first (e.g., a teaspoon of honey in patients aged 1 year and older).

» Consider short-term use of an oral opioid in adults if the cough is distressing to the patient. Codeine (linctus or tablet) is the preferred first-line option, with oral morphine solution reserved as a second-line option.[282]

# Emerging

## Introduction

No treatments have been approved or shown to be safe and effective for the treatment of COVID-19. However, 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.[333] [334] [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.[335] 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).[336] [Global coronavirus COVID-19 clinical trial tracker]

## 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). Clinical trials with remdesivir have started in patients with mild to severe COVID-19.[337] [338] [339] [340] [341] [342] [343] It has been used on a compassionate-use basis in areas where clinical trials are not available; however, the manufacturer has paused access to the drug via this route due to overwhelming demand while they transition to an expanded access programme. Exceptions will be made for patients with severe illness, and pregnant women and children with confirmed infection.[344] It appears to be safe to use in pregnancy.[326] The EMA has published recommendations on compassionate use of remdesivir for COVID-19.[345] 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.[346] 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.[347] The National Institutes of Health has reported preliminary findings from a randomised, placebo-controlled trial of remdesivir in 1063 patients hospitalised with severe COVID-19. The study found that patients taking remdesivir had a 31% faster time to recovery (i.e., being well enough for discharge or returning to normal activity level) compared with placebo, with a median recovery time of 11 days versus 15 days, and the mortality rate was 8% with remdesivir compared with 11.6% with placebo. The findings are yet to be peer reviewed.[348] The manufacturer has issued a press release announcing preliminary findings from an open-label, phase 3 trial, reporting that a 5-day course is as safe and efficacious as a 10-day course.[349] There is currently insufficient evidence to recommend either for or against the use of remdesivir for the treatment of COVID-19.[288]

## 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.[337] [350] They are being trialled in patients for the treatment of mild to severe COVID-19.[351] [352] [353] They are also being trialled for prevention and post-exposure prophylaxis in the healthcare setting.[354] [355] Initial data is promising, but is currently limited. 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.[356] However, this trial has been criticised for its limitations, and results from a similar trial could not replicate these findings.[357] [358] 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.[359] 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 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).[360] Hydroxychloroquine has similar therapeutic effects to chloroquine, but fewer adverse effects, is considered safe in pregnancy, and is more readily available in some countries.[361] Both drugs must be used with caution in patients with pre-existing cardiovascular disease due to the risk of arrhythmias.[362] Because chloroquine/hydroxychloroquine and azithromycin can both cause QT interval prolongation, caution is recommended when using these drugs together. 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.[363] This combination is not recommended except in the context of a clinical trial.[288] Caution is recommended with the dosing regimen used for chloroquine due to the risk of chloroquine poisoning.[364] 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.[365] Guidelines in China and Italy recommend these drugs for the treatment of COVID-19; however, this is based on weak evidence.[366] 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.[284] [288] 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.[314] 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.[367] In the US, the Food and Drug Administration (FDA) has granted an emergency-use authorisation for chloroquine and hydroxychloroquine to treat patients when a clinical trial is not available or participation is not feasible.[368] 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.[369] There is currently no strong evidence of efficacy of hydroxychloroquine or chloroquine in the treatment or prevention of COVID-19. [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.[370] A randomised controlled trial of approximately 200 patients in China found that treatment with lopinavir/ritonavir was not beneficial compared with standard care alone (primary outcome was time to improvement) in hospitalised patients with severe COVID-19.[371] It is considered safe in pregnancy.[326] 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.[288] [Centre for Evidence-Based Medicine: lopinavir/ritonavir - a rapid review of effectiveness in COVID-19]

## 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.[372] Clinical trials to determine the safety and efficacy of convalescent plasma that contains antibodies to SARS-CoV-2 in patients with COVID-19 have started.[373] A small preliminary case series of five critically ill patients reported clinical improvement after treatment with convalescent plasma; however, this study had many limitations.[374] Another study of 10 patients with severe illness in China noted symptomatic improvement within 3 days. Viral load was undetectable within 7 days in 70% of patients. No serious adverse reactions were noted.[375] 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 (for at least 2 weeks) to donate their plasma.[376] [377] [378] There is currently insufficient evidence to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.[288]

## 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.[379]

## Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is being trialled in some patients with COVID-19.[26] [380] Novel multi-antibody cocktail therapies are also in development for prophylaxis or treatment.[381] 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.[382] There is currently insufficient evidence to recommend either for or against the use of IVIG for the treatment of COVID-19.[288]

## 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.[383] [384] [385] [386] [387] [388] [389] [390] 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.[391] 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 and baricitinib, and the C-C chemokine receptor type 5 (CCR5) antagonist leronlimab.[392] [393] [394] 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.[288]

## 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.[395] 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.[396]

## 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.[397]

## 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.[398] [399] [400] However, some experts believe that these drugs may worsen COVID-19 due to

overexpression of ACE2 in people taking these drugs. See Management Approach for a discussion of the controversy.

## 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 alfa, nebulised interferon beta).[401] [402] [403] [404] [405] [406] [407] [408] [409] 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.[410]

## Vitamin C

Vitamin C supplementation has shown promise in the treatment of viral infections.[411] High-dose intravenous vitamin C is being trialled in some centres for the treatment of severe COVID-19.[412]

## Vitamin D

Vitamin D supplementation has been associated with a reduced risk of respiratory infections such as influenza in some studies.[413] [414] [415] It has been suggested that there may be an association between vitamin D status and COVID-19 severity; however, there is no evidence to support this association and further research is needed.[416] [417] [418] [419] Vitamin D is being trialled in patients with COVID-19.[420] [421] 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.[422] There is no evidence to recommend vitamin D for the prophylaxis or treatment of COVID-19.

## 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.[423]

FOLLOW UP

# Recommendations

## Monitoring

Monitor vital signs (i.e., temperature, respiratory rate, heart rate, blood pressure, oxygen saturation) and perform haematology and biochemistry laboratory testing and ECG as clinically indicated during admission. Utilise medical early warning scores that facilitate early recognition and escalation of treatment of deteriorating patients (e.g., National Early Warning Score 2 [NEWS2]) where possible.[3] However, there are no data on the value of using these scores in patients with COVID-19 in the primary care setting.[517] A new prediction score for COVID-19 progression risk has been proposed (the CALL score), but it has not been validated as yet.[518]

Monitor coagulation parameters (e.g., D-dimer, fibrinogen, platelet count, prothrombin time) to identify worsening coagulopathy.[519]

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.[328]

Perform molecular testing regularly during admission. Two consecutive negative tests (at least 24 hours apart) are required in a clinically recovered patient before discharge.[3] However, it is important to note that the rate of false-negative tests appears to be high, and patients are retesting positive after discharge; therefore, these measures may not be stringent enough to ensure patients are no longer contagious.[520]

## 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).[143] [144]
- [BMJ Learning: Covid-19 - handwashing technique and PPE videos]
- [WHO: coronavirus disease (COVID-19) advice for the public]

Face masks

- The World Health Organization recommends that people with symptoms should wear a medical mask, self-isolate, and seek medical advice as soon as possible. Masks are also recommended for those caring for a sick person at home when in the same room. 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.[146] [150]
- 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.[147]
- [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 and exemptions]
  - [Ministry of Manpower Singapore: advisories on COVID-19]

Pets

- At this time, there is no evidence that companion animals (including pets and other animals) can spread COVID-19 or that they might be a source of infection, but caution is advised until more information is available.[521]
- 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. A tiger tested positive in a zoo in New York.[521] [522] 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.[523] Two pet cats have tested positive in New York.[524]
- 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.[521]
- [CDC: coronavirus disease 2019 (COVID-19) - if you have animals]

Resources

- [WHO: coronavirus disease (COVID-19) pandemic]
- [WHO: stay physically active during self-quarantine]

- [CDC: coronavirus (COVID-19)]
- [NHS UK: coronavirus (COVID-19)]

 

FOLLOW UP

# Complications

| Complications | Timeframe | Likelihood |
|---|---|---|
| **comorbidities** | **short term** | **high** |
| Data on the management of comorbidities in patients with COVID-19 is evolving rapidly. Tailor the management of critical illness 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).[3]<br><br>People who are taking ACE inhibitors, angiotensin receptor antagonists, statins, inhaled or oral corticosteroids, or nonsteroidal anti-inflammatory drugs for a pre-existing comorbid condition should continue on these medications as directed by their physician.[288]<br><br>For more information, see the Best Practice topic: Management of coexisting conditions in the context of COVID-19. | | |
| **acute respiratory distress syndrome (ARDS)** | **short term** | **medium** |
| Reported in 15% to 33% of patients in case series.[25] [26] [45] [170] [212]<br><br>Children can quickly progress to ARDS.[16]<br><br>Factors that increase the risk of developing ARDS and death include older age, neutrophilia, elevated lactate dehydrogenase levels, and elevated D-dimer levels.[453]<br><br>Lung transplant has been reported in a small number of cases in China as the sole therapy for end-stage pulmonary fibrosis related to ARDS in COVID-19 patients.[454] | | |
| **acute respiratory failure** | **short term** | **medium** |
| Reported in 8% of patients in case series.[26]<br><br>Leading cause of mortality in patients with COVID-19.[438]<br><br>Children can quickly progress to respiratory failure.[16] | | |
| **cardiovascular complications** | **short term** | **medium** |
| COVID-19 is associated with a high inflammatory burden that can result in cardiovascular complications with a variety of clinical presentations. Inflammation in the 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.[455] [456] [457] These complications can present on presentation or develop as the severity of illness worsens.[458] 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.[459]<br><br>Acute myocardial injury has been reported in 7% to 20% of patients in case series, and is indicated by elevated cardiac biomarkers.[25] [45] [212] [460] Prevalence is high among patients who are severely or critically ill, and these patients usually require intensive care and have a higher rate of in-hospital mortality. Patients with cardiac injury were more likely to require non-invasive or invasive ventilation compared with patients without cardiac injury.[458] [460] [461] [462] Patients with underlying cardiovascular disease but without myocardial injury have a relatively favourable prognosis.[463]<br><br>Cases of fulminant myocarditis, cardiomyopathy, cardiac tamponade, myopericarditis with systolic dysfunction, pericarditis and pericardial effusion, ST-segment elevation (indicating potential acute | | |

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

myocardial infarction), and takotsubo syndrome have been reported.[436] [438] [464] [465] [466] [467] [468]

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.[469]

Monitor blood pressure, heart rate, and fluid balance, and perform continuous ECG monitoring in all patients with suspected or confirmed acute myocardial injury.[469]

There are limited data to recommend any specific drug treatments for these patients. Management should involve a multidisciplinary team including intensive care specialists, cardiologists, and infectious disease specialists.[459] It is important to consider that drugs such as hydroxychloroquine and azithromycin may prolong the QT interval and lead to arrhythmias.[469]

Infection may have longer-term implications for overall cardiovascular health; however, further research is required.[470]

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

Approximately 76% of patients had abnormal liver test results in one study.[471] Acute liver injury has been reported in 14% to 53% of patients in case series. Occurs more commonly in patients with severe disease.[472] Although data support a higher prevalence of abnormal aminotransferase levels in patients with severe illness, evidence suggests that clinically significant liver injury is uncommon.[473] [474] Medications (e.g., lopinavir/ritonavir) may have a detrimental effect on liver injury.

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

Cytokine release syndrome may cause ARDS or multiple-organ dysfunction, which may lead to death.[475] 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.[25] [251] [442] [476] Interleukin-6, in particular, has been associated with severe COVID-19 and increased mortality.[444]

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.[477]

Anti-inflammatory/immunosuppressive treatments (e.g., tocilizumab, hydroxychloroquine/chloroquine, Janus kinase inhibitors) are being trialled in COVID-19 patients.[478] See our Emerging section for more information.

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

Reported in 4% to 8% of patients in case series.[25] [26] [45] [212]

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.[284] [288] 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

 

| Complications | Timeframe | Likelihood |
|---|---|---|
| fluid loading and the use of vasopressors. Low-dose corticosteroid therapy is recommended for refractory shock.[288] | | |
| **disseminated intravascular coagulation** | **short term** | **low** |
| Reported in 71% of non-survivors.[249] 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.[479]<br><br>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.[480]<br><br>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 (see below).[481] Anticoagulant therapy with a low molecular weight heparin or unfractionated heparin has been associated with a better prognosis in patients with severe COVID-19 who have a sepsis-induced coagulopathy (SIC) score of ≥4 or a markedly elevated D-dimer level.[482] In patients with heparin-induced thrombocytopenia (or a history of it), argatroban or bivalirudin are recommended.[479]<br><br>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.[480] [481] | | |
| **venous thromboembolism** | **short term** | **low** |
| Coagulopathy in COVID-19 has a prothrombotic character, which may explain reports of thromboembolic complications.[483] 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).[484]<br><br>Venous thromboembolism has been reported in 25% to 69% of patients with severe COVID-19 in the intensive care unit, and may be associated with poor prognosis.[485] [486] [487]<br><br>Acute pulmonary embolism on CT angiography has been reported in 23% of patients in one US centre, and 20% to 30% of patients in France. These patients were more likely to require critical care and mechanical ventilation compared with patients without pulmonary embolism. A D-dimer threshold of 2660 micrograms/L detected all patients with pulmonary embolism in the French study.[488] [489] [490]<br><br>Identifying patients with COVID-19 who are at high risk is important so that venous thromboembolism prophylaxis measures (pharmacological or mechanical thromboprophylaxis) can be instituted.[491] Low molecular weight heparin is preferred over unfractionated heparin in order to reduce patient contact (depending on the patient's bleeding risk and creatinine clearance). Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia.[492] Direct oral anticoagulants can interact with the experimental antivirals used to treat COVID-19; therefore, consider switching patients on these medications to a suitable alternative parenteral anticoagulant during treatment until discharge.[493]<br><br>The optimal anticoagulant dose in COVID-19 in patients is unknown. Some clinicians are using intermediate- or full-dose regimens rather than prophylactic doses as they are worried about undetected thrombi; however, this may lead to major bleeding events.[484] 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).[491] | | |
| **secondary infection** | **short term** | **low** |

| Complications | Timeframe | Likelihood |
|---|---|---|
| Reported in 6% to 10% of patients in case series.[25] [212]<br><br>A case of *Staphylococcus aureus* superinfection has been reported.[494] | | |
| **acute kidney injury** | **short term** | **low** |
| Reported in 3% to 8% of patients in case series.[25] [26] [212] A large prospective cohort study of over 700 patients in China found that over 40% of patients with COVID-19 had proteinuria on admission, and 26% had haematuria. Approximately 13% to 14% of patients had elevated creatinine, elevated urea, and an estimated glomerular filtration rate <60 mL/minute/1.73 m². During the study, acute kidney injury developed in 5% of patients, and these patients had an increased risk of in-hospital mortality.[495] However, a retrospective study of 116 hospitalised patients in Wuhan found that the few patients who had elevated urea, serum creatinine, or albuminuria did not meet the diagnostic criteria for acute kidney injury.[496] | | |
| **pancreatic injury** | **short term** | **low** |
| Mild pancreatic injury (defined as elevated serum amylase or lipase levels) has been reported in 17% of patients in one case series. 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.[497] | | |
| **neurological complications** | **short term** | **low** |
| Patients with severe illness commonly have neurological complications, likely due to viral invasion of the central nervous system (SARS-CoV-2 has been detected in the brain and cerebrospinal fluid). In a case series of 214 patients, neurological symptoms were seen in 36% of patients, and were more common in patients with severe illness.[498]<br><br>Complications include acute cerebrovascular disease, impairment of consciousness, ataxia, seizures, neuralgia, skeletal muscle injury, corticospinal tract signs, meningitis, encephalitis, and encephalopathy. Patients may present with these signs/symptoms, or they may develop them during the course of the disease. These patients have a poor prognosis.[498] [499] [500] [501] [502] [503] [504]<br><br>Large-vessel stroke has been reported in a small number of patients younger than 50 years of age in New York.[505]<br><br>Cases of COVID-19 initially presenting with acute Guillain-Barre syndrome have been reported in patients with COVID-19.[506] [507] [508] [509] | | |
| **rhabdomyolysis** | **short term** | **low** |
| Reported as a late complication in one case report.[510] | | |
| **pregnancy-related complications** | **short term** | **low** |
| Retrospective reviews of pregnant women with COVID-19 found that women appeared to have fewer adverse maternal and neonatal complications and outcomes than would be expected for those with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). Adverse effects on the newborn including fetal distress, 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. No maternal deaths have been reported so far, but miscarriage (including a case in the second trimester), ectopic pregnancy, intrauterine growth restriction, perinatal death, and preterm birth have been reported. It is unclear whether this is related to COVID-19.[84] [85] [90] [326] [511] [512] [513] [514] | | |

 

FOLLOW UP

| Complications | Timeframe | Likelihood |
|---|---|---|
| **aspergillosis** | **short term** | **low** |
| Invasive pulmonary aspergillosis has been reported in critically ill patients with moderate to severe ARDS.[515] [516]<br><br>Intubation for more than 7 days may be a risk factor. Potential contributing factors include 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.[313] | | |

# 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 7% based on World Health Organization data as of 30 April 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 the US, Germany, Australia, Turkey, Iceland, and Singapore.[424]

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).[7] 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).[425]

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%.[426] [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.[427]

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.[426] [428]

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%).[25] Despite the lower CFR, COVID-19 has so far resulted in more deaths than both SARS and MERS combined.[429]

## 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.[430]

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 (0.1% to 0.5%). 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.

- 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.[431]
- 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.[432]
- Santa Clara county, California: an analysis of 3300 people in early April found that the seroprevalence of antibodies to severe acute respiratory syndrome coronavirus 2 (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.[433]
- Iceland: the country where the most testing per capita has occurred - the IFR lies between 0.01% and 0.19%.[426]

These estimates are likely to change as more data emerge.

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

The CFR increases with age.[425] 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.[434]

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).[7] 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.[425]

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.[118] 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%.[435]

In the US, the CFR was highest among patients aged ≥85 years (10% to 27%), followed by those aged 65 to 84 years (3% to 11%), 55 to 64 years (1% to 3%), 20 to 54 years (<1%), and ≤19 years (no deaths). Patients

 

aged ≥65 years accounted for 80% of deaths.[10] 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.[436] The CFR in residents in a long-term care facility in Washington was reported to be 34%.[437]

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

## Prognostic factors

The leading cause of death in patients with COVID-19 is respiratory failure from acute respiratory distress syndrome.[438] Patients who required invasive mechanical ventilation had an 88% mortality rate in one study.[115] The other most common complications in deceased patients are myocardial injury, liver or kidney injury, and multi-organ dysfunction.[439] 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.[440]

Prognostic factors that have been associated with disease progression to severe or critical illness or even death include:[104] [245] [247] [441] [442] [443] [123] [444]

- Older age ≥65 years
- Male sex
- Smoking
- Presence of comorbidities (e.g., hypertension, diabetes, cardiovascular or cerebrovascular disease, respiratory disease)
- Dyspnoea
- Hypoxaemia
- Lymphopenia
- Leukocytosis
- Thrombocytopenia
- High neutrophil-to-lymphocyte ratio
- Decreased albumin level
- Liver or kidney impairment
- Elevated lactate dehydrogenase
- Elevated inflammatory markers (C-reactive protein, procalcitonin)
- Elevated cardiac troponin I
- Elevated D-dimer
- Decreased CD3+, CD4+, or CD8+ T cells
- Elevated interleukin-6
- Higher Sequential Organ Failure Assessment (SOFA) score.

## 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.[445]

## 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.[446] [447]

## Reinfection/relapse/reactivation

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reactivation has been reported in patients after hospital discharge. In a retrospective review of 55 patients in China, 9% of patients presented with SARS-CoV-2 reactivation. The clinical characteristics were similar to those of non-reactivated patients.[448] Other studies have shown that 10% to 21% of patients return a positive reverse-transcription polymerase chain reaction (RT-PCR) test again after two negative RT-PCR tests and after hospital discharge.[449] [450] [451] 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.[452] Further research is required.

## Future immunity

There are no data available yet on whether patients have immunity from reinfection after recovery.

# Diagnostic guidelines

## Europe

### COVID-19: guidance for health professionals

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

### COVID-19

**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

## North America

### Coronavirus disease 2019 (COVID-19): information for laboratories

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

### Interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings

**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

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

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

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

### Guideline for the treatment of people with COVID-19 disease

**Published by:** Italian Society of Infectious and Tropical Diseases **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 severe acute respiratory infection (SARI) when COVID-19 disease is suspected

**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

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

**Published by:** World Health Organization **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 2019 novel coronavirus infection during pregnancy and puerperium: information for healthcare professionals

**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 COVID-19 patients

**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

### Ending home isolation for immunocompromised persons with COVID-19

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

### Discontinuation of isolation for persons with COVID-19 not in healthcare settings (interim guidance)

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

### Interim U.S. guidance for risk assessment and public health management of healthcare personnel with potential exposure in a healthcare setting to patients with coronavirus disease (COVID-19)

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

### Coronavirus disease 2019 (COVID-19): considerations for inpatient obstetric healthcare settings

**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 infection

**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

# North America

## Management of infants born to mothers with 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. WHO: coronavirus disease (COVID-19) emergency dashboard *(external link)*
4. WHO: coronavirus disease (COVID-2019) situation reports *(external link)*
5. CDC: cases of coronavirus disease (COVID-19) in the US *(external link)*
6. CDC: COVIDView *(external link)*
7. GenBank *(external link)*
8. BMJ Learning: Covid-19 - handwashing technique and PPE videos *(external link)*
9. WHO: coronavirus disease (COVID-19) advice for the public *(external link)*
10. BMJ: facemasks for the prevention of infection in healthcare and community settings *(external link)*
11. BMJ: analysis - face masks for the public during the covid-19 crisis *(external link)*
12. WHO: coronavirus disease (COVID-19) advice for the public - when and how to use masks *(external link)*
13. Public Health England: guidance on social distancing for everyone in the UK *(external link)*
14. Public Health England: guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19 *(external link)*
15. BMJ: covid-19 in primary care (UK) *(external link)*
16. BMJ: covid-19 - a remote assessment in primary care *(external link)*
17. BMJ: covid-19 - PPE guidance *(external link)*
18. WHO: infection prevention and control during health care when COVID-19 is suspected *(external link)*
19. CDC: interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings *(external link)*
20. CDC: strategies to optimize the supply of PPE and equipment *(external link)*
21. BSTI: radiology decision tool for suspected COVID-19 *(external link)*
22. BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas *(external link)*

23. WHO: global surveillance for COVID-19 caused by human infection with COVID-19 virus *(external link)*

24. CDC: evaluating and testing persons for coronavirus disease 2019 (COVID-19) *(external link)*

25. CDC: priorities for testing patients with suspected COVID-19 infection *(external link)*

26. IDSA: COVID-19 prioritization of diagnostic testing *(external link)*

27. BMJ talk medicine podcast: coping with Covid-19 - advice from a New York City intensivist *(external link)*

28. Clinical frailty scale *(external link)*

29. WHO: home care for patients with COVID-19 presenting with mild symptoms and management of their contacts *(external link)*

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

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

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

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

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

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

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

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

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

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

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

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

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

43. Government of Canada: coronavirus disease (COVID-19) - travel restrictions and exemptions *(external link)*

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

45. CDC: coronavirus disease 2019 (COVID-19) - if you have animals *(external link)*

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

47. WHO: stay physically active during self-quarantine *(external link)*

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

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



 

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# Images



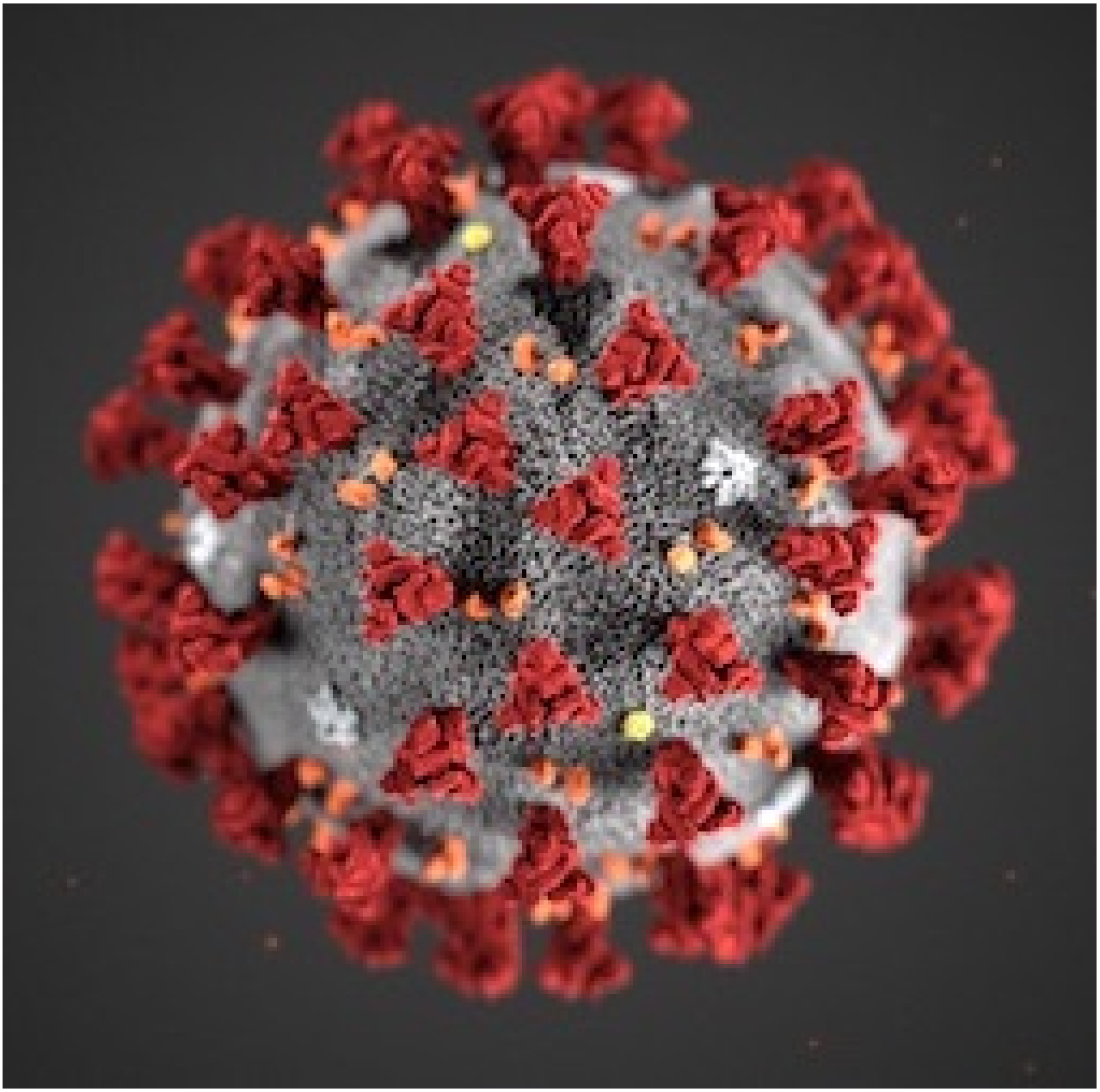

*Figure 1: Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically*

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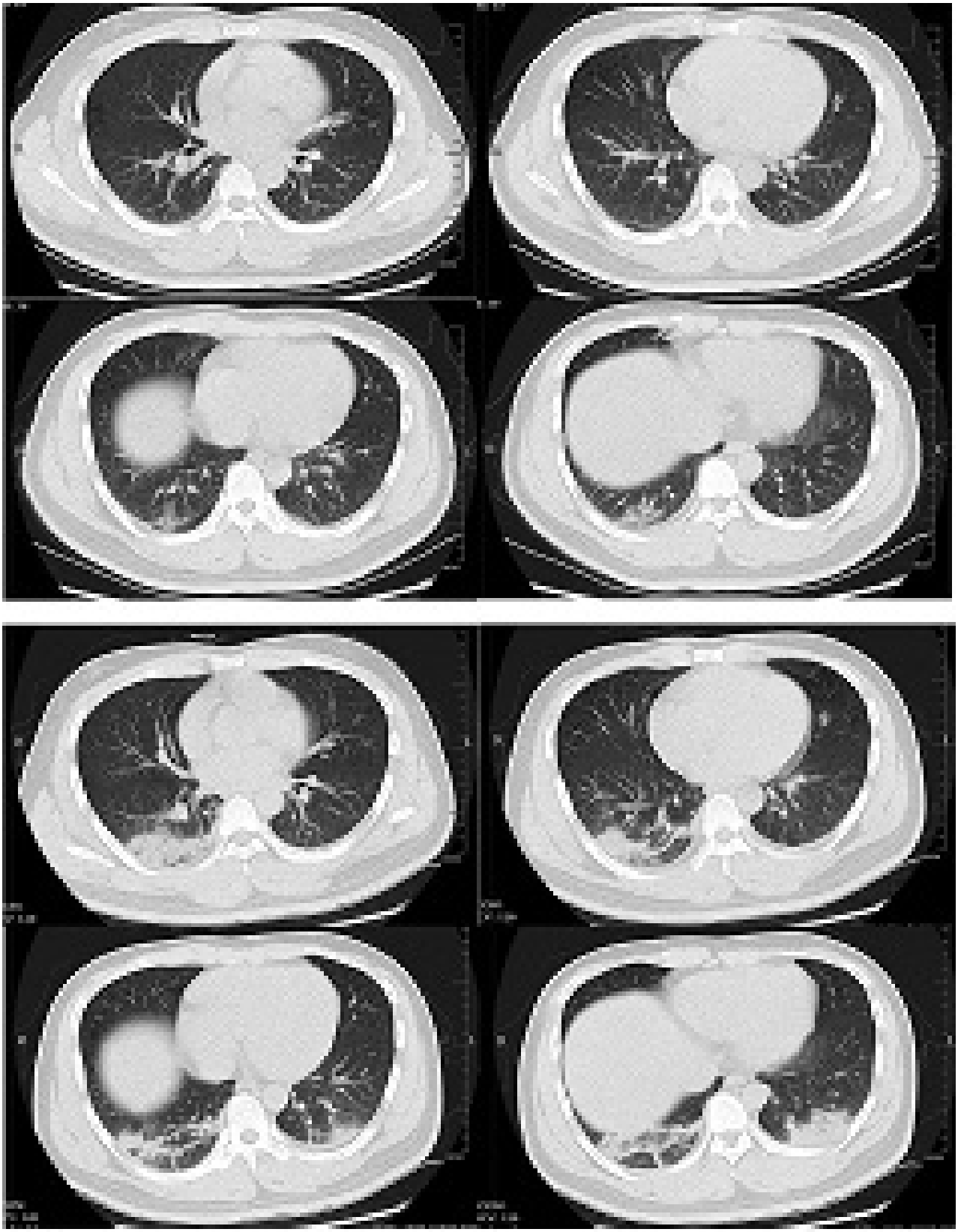

*Figure 2: Transverse CT scans from a 32-year-old man, showing ground-glass opacity and consolidation of lower lobe of right lung near the pleura on day 1 after symptom onset (top panel), and bilateral ground-glass opacity and consolidation on day 7 after symptom onset*

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