BMJ Best Practice

Coronavirus disease 2019 (COVID-19)

The right clinical information, right where it's needed

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Summary

- The situation is evolving rapidly with global case counts and deaths increasing each day. The World Health Organization declared the COVID-19 outbreak a pandemic on 11 March 2020 and rates the global risk assessment as very high. 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). The virus was identified as the cause of an outbreak of pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019.[1] 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.

The International Committee on Taxonomy of Viruses has confirmed SARS-CoV-2 as the name of the virus owing to the virus's genetic similarity to the SARS-CoV virus, but taking into account that there may be differences in disease spectrum and transmission.[2] [3] The World Health Organization has confirmed COVID-19 (a shortened version of coronavirus disease 2019) as the name of the disease that SARS-CoV-2 infection causes.[4] Prior to this, the virus and/or disease was known by various names including novel coronavirus (2019-nCoV), 2019-nCoV, or variations on this.

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).[6] 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.[7] 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:

- [WHO: novel coronavirus (COVID-19) situation dashboard]
- [WHO: coronavirus disease (COVID-2019) situation reports]
- [CDC: coronavirus disease 2019 (COVID-19) – cases in US]
- [CDC: locations with confirmed COVID-19 cases, by WHO region]

Data from the largest case series in China to date (72,314 cases from 31 December 2019 to 11 February 2020) found that the majority of confirmed cases (87%) 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. Nearly 4% of cases were in healthcare workers.[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 being reported much less commonly than among adults. A systematic review found that children accounted for 1% to 5% of confirmed cases (depending on the country) so far.[11] All cases so far have been in family clusters or in children who have a history of close contact with an infected patient.[12]

[13] [14] In a case series of 2143 paediatric patients in China, the median age of children was 7 years, and 56.6% of cases were in boys although this gender difference was not considered significant.[15]

Emerging evidence suggests that cold and dry conditions may facilitate the spread of COVID-19; however, further research is required on how weather conditions influence transmission.[16]

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.[1] Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, SARS, MERS), and others that circulate among mammals (e.g., bats, camels) 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 severe acute respiratory syndrome (SARS)-like coronaviruses from bats, but it is distinct from SARS-CoV and Middle East respiratory syndrome (MERS)-CoV.[17] [18] 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.[19]

[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.[20] [21] [22]
- 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.[17] [18] [23] [24] Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses.[25] [26]

Transmission dynamics

- Transmission dynamics of the virus are currently unknown and the situation is rapidly evolving. Person-to-person spread has been confirmed in community and healthcare settings, with local transmission reported in many countries around the world.
- It is uncertain how easily the virus spreads between people, but transmission in chains involving several links is increasingly recognised. Available evidence indicates that human transmission occurs via close contact with respiratory droplets produced when a person exhales, sneezes, or coughs, or

via contact with fomites. Airborne transmission has not been reported; however, it may be possible during aerosol-generating procedures performed in clinical care.[20] [22] [27] [28]

- 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).[29] 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.[30]
- The contribution to transmission by the presence of the virus in other body fluids is unknown; however, the virus has been detected in blood, saliva, tears, cerebrospinal fluid, and conjunctival secretions. Faecal-oral transmission may be possible, although it has not been reported yet.[31] [32] [33] [34] [35] [36]
- 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. One study of a family cluster of five patients in Shenzhen who had a history of travel to Wuhan City (with one other family member who did not travel to Wuhan City) found that person-to-person spread is possible in both hospital and family settings.[22]
- Nosocomial transmission in healthcare workers and patients has been reported in 41% of patients in one case series.[37]
- Widespread transmission has been reported in long-term care facilities and on cruise ships (19% of 3700 passengers and crew were infected aboard the Diamond Princess).[38] [39]

Asymptomatic transmission

- 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.[40] However, a Japanese study of citizens evacuated from Wuhan City estimates the rate to be closer to 31%.[41] Early data from an isolated village of 3000 people in Italy estimates the figure to be higher at 50% to 75%.[42]
- The proportion of asymptomatic cases in children is thought to be significant, and children may play a role in community spread.[43]
- There is mounting evidence that spread from asymptomatic carriers can occur and this has been observed in endemic areas.[44] [45] [46] [47] [48] [49] Presymptomatic transmission has been reported in 12.6% of cases in one study.[50]

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.[51]
- 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.[52] [53]
- 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.[52]

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.[54] [55] However, vertical transmission cannot be ruled out. 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.[56] [57] [58] [59] [60]

Pathophysiology

Incubation period

- Current estimates of the incubation period range from 1 to 14 days, according to the World Health Organization and the US Centers for Disease Control and Prevention.[61] [62]
- The median incubation period has been estimated to be approximately 5 days.[22] [63] However, a pre-print study (not peer reviewed) suggests that the median incubation period may be longer (7 days in adults and 9 days in children with a range of 0 to 33 days).[64]
- Transmission may be possible during the incubation period.[65]

Reproductive number

- Preliminary reports suggest that the reproductive number (R_0), the number of people who acquire the infection from an infected person, is approximately 2.2.[22] [66] However, as the situation is still evolving, the R_0 may actually be higher or lower.
- The secondary attack rate for SARS-CoV-2 is estimated to be 0.45% for close contacts of US patients.[28]

Angiotensin-converting enzyme-2 receptor

- While the pathophysiology of this condition is currently unknown, it is thought that the virus binds to the angiotensin-converting enzyme-2 (ACE2) receptor in humans, which suggests that it may have a similar pathogenesis to SARS.[18] [67] 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.[68] A furin-like cleavage site has been identified in the spike protein of the virus; this does not exist in other SARS-like coronaviruses.[69]
- 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.[70]
- 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.[71]

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.[72] [73]

- The median duration of viral shedding is approximately 20 days in survivors.[74]

Classification

World Health Organization: clinical classification of COVID-19[5]

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:[82] [83]
    - Wash hands often with soap and water or an alcohol-based hand sanitiser and 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]), particularly those who have a fever or are coughing or sneezing
    - 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 with their healthcare provider
    - Avoid direct unprotected contact with live animals and surfaces in contact with live animals when visiting live markets in affected areas
    - Avoid the consumption of raw or undercooked animal products, and handle raw meat, milk, or animal organs with care as per usual good food safety practices.
- [WHO: coronavirus disease (COVID-19) advice for the public]

Medical masks

- Recommendations on the use of face masks in community settings vary between countries.[84]
- The World Health Organization (WHO) does not recommend that people wear a medical mask in community settings if they do not have respiratory symptoms as there is no evidence available on their usefulness to protect people who are not ill. However, masks may be worn in some countries according to local cultural habits. Individuals with fever and/or respiratory symptoms are advised to wear a mask and seek medical care as soon as possible. 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.[85] [86]
- It is mandatory to wear a medical mask in public in certain areas of China, and local guidance should be consulted for more information.
- It is important to wash your hands with soap and water (or an alcohol-based sanitiser) prior to putting on a face mask.[87]
- [BMJ: facemasks for the prevention of infection in healthcare and community settings]

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 an incubation period, which may exceed 10 days.[88] 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.[89]
- Enforced quarantine has been used in some countries to isolate easily identifiable cohorts of people at potential risk of recent exposure (e.g., groups evacuated by aeroplane from affected areas, or groups

on cruise ships with infected people on board).[90] The psychosocial effects of enforced quarantine may have long-lasting repercussions.[91] [92]

Social distancing

- Many countries are implementing mandatory social distancing measures in order to reduce and delay transmission (e.g., city lockdowns, school and university closures, screening measures at airports and train stations, restriction of movement, remote working, quarantine of exposed people). Although the evidence for social distancing for COVID-19 is limited, it is emerging, and the best available evidence appears to support social distancing measures to reduce the transmission and delay spread. The timing and duration of these measures appears to be critical.[93] [94]
- Researchers in Singapore found that social distancing measures (isolation of infected individuals and family quarantine, school closures, and workplace distancing) significantly decrease the number of infections in simulation models.[95]

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:[96]
    - 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 defined on medical grounds as extremely vulnerable from COVID-19]

Vaccine

- There is currently no vaccine available. Vaccines are in development, but it may take some time before a vaccine is available.[97] [98] [99] An mRNA vaccine (mRNA-1273) has been shipped to the National Institute of Allergy and Infectious Diseases for phase 1 clinical trials in the US.[100] The vaccine includes a short segment of genetic code copied from the virus. The trial started in humans on 16 March 2020. The vaccine is being fast-tracked and has skipped the animal testing stage. Clinical trials in humans have also started on an experimental adenoviral vector vaccine in China.[101]

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:[155]

- 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 returning travellers to enter quarantine. Travellers who develop symptoms are advised to contact their local health care provider, preferably by phone.[156]

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.[157]

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.[104] 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 on 3 March 2020 with fever, cough, and difficulty breathing. He also reports feeling very tired and unwell. He has a history of congestive heart failure, which is controlled with medication. On examination, his pulse is 120 bpm and his temperature is 38.7°C (101.6°F). Chest x-ray shows bilateral lung infiltrates. He is admitted to hospital in an isolation room and is started on oxygen, intravenous fluids, empirical antibiotics, and paracetamol. Later that day, he tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on real-time reverse transcriptase polymerase chain reaction testing. The patient develops respiratory distress 7 days after admission and is started on mechanical ventilation.

Case history #2

A 30-year-old man presents to his general practitioner on 14 January 2020 with a bad cough. He has had the cough for 4 days and now feels a little short of breath. He also has a headache and reports that his muscles ache. On examimation, his pulse is 100 bpm and his temperature is 38.5°C (101.3°F). The patient reports that he returned from a business trip in mainland China 6 days ago.

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 report a travel history to an affected area 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.[102] Most patients can be managed remotely by telephone or video consultations.[103] 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. 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.

The World Health Organization (WHO) recommends the following basic principles:[104]

- 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.[105] [106]

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.[107]

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 for optimizing the supply of PPE]

History

Take a detailed history to ascertain the level of risk for COVID-19 and assess the possibility of other causes. Travel history may be key; it is crucial for timely diagnosis and to prevent further transmission.

Diagnosis should be suspected in:[75]

- 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.[9] Atypical presentations may occur, especially in older patients or patients who are immunocompromised.

Severe illness is associated with older age and the presence of underlying health conditions.[9] [76] Older patients and/or those with comorbidities may present with mild symptoms, but have a high risk of deterioration.[5]

The most common symptoms are:[20] [21] [37] [108] [109] [110]

- Fever
- Cough
- Dyspnoea
- Myalgia
- Fatigue.

Less common symptoms include:

- Anorexia
- Sputum production
- Sore throat
- Confusion
- Dizziness
- Headache
- Rhinorrhoea
- Chest pain
- Haemoptysis
- Diarrhoea
- Nausea/vomiting
- Abdominal pain
- Anosmia/dysgeusia

- Conjunctival congestion
- Cutaneous manifestations.

Approximately 90% of patients present with more than one symptom, and 15% of patients present with fever, cough, and dyspnoea.[21] 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.[5]

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.[111]

Co-infections (e.g., influenza, human metapneumovirus) have been reported. Patients with influenza co-infection showed similar characteristics to those patients with COVID-19 only.[74] [112] [113]

Perform a physical examination. 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., brief and rapidly resolving fever, mild cough, sore throat, congestion, rhinorrhoea).[12] [13] [114] [115] [116] However, moderate to severe illness has also been reported in children.[117] Polypnoea has been reported in children with severe illness.[118] There are case reports of neonates and infants presenting with predominantly gastrointestinal symptoms.[119] [120]

In a case series 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.[15] However, it is important to note that children may have signs of pneumonia on chest imaging despite having minimal or no symptoms.[121]

Co-infections may be more common in children.[121] 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.[54] [57] 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.[5]

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 (serum procalcitonin and C-reactive protein)
- Serum troponin
- Serum lactate dehydrogenase
- Serum creatine kinase.

The most common laboratory abnormalities in patients hospitalised with pneumonia include leukopenia, lymphopenia, leukocytosis, elevated liver transaminases, elevated lactate dehydrogenase, and elevated C-reactive protein. Other abnormalities include neutrophilia, thrombocytopenia, decreased haemoglobin, decreased albumin, and renal impairment.[20] [21] [37] [110] [122]

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

[VIDEO: Radial artery puncture animated demonstration]

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.[5]

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.[5] 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in appropriate patients with suspected infection, with confirmation by nucleic acid sequencing when necessary.[123]

- 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.[123] 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.[124]

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.[5] [125]

Serological testing is not available as yet, but assays are in development.[126] Serum samples can be stored to retrospectively define cases when validated serology tests become available. Early data indicate continuous high levels of immunoglobulin M (IgM) during the acute phase of infection, with IgM lasting more than 1 month (indicating prolonged virus replication in infected patients). IgG responded later than IgM.[127]

Imaging

All imaging procedures should be performed according to local infection prevention and control procedures to prevent transmission.

Chest x-ray

- 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.[20] [21] [128]

CT chest

- Consider ordering a CT scan of the chest. Abnormal chest CT findings have been reported in up to 97% of patients in one meta-analysis of 50,466 hospitalised patients.[109] CT is the primary imaging modality in China.[129]
- CT imaging generally shows bilateral multiple lobular and subsegmental areas of ground-glass opacity or consolidation 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. Other atypical features include interlobular or septal thickening (smooth or irregular), thickening of the adjacent pleura, subpleural involvement, crazy paving pattern, and air bronchograms. 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. None of these findings appear to be specific or diagnostic for COVID-19.[20] [111] [130] 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.[131] 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.[130] 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.[132]

- Small nodular ground-glass opacities are the most common finding in children.[133] Consolidation with surrounding halo signs is a typical finding in children.[121]
- Evidence of viral pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[126] However, CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients.[47] [131] Some patients may present with a normal chest finding despite a positive RT-PCR.[134]
- 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.[135]

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.[75]
- [WHO: novel coronavirus (COVID-19) situation dashboard]
- [CDC: locations with confirmed COVID-19 cases, by WHO region]

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.[75]

older age and/or underlying health condition

- 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.[76]
- The most prevalent comorbidities in patients with COVID-19 are hypertension, diabetes, cardiovascular disease, and respiratory disease.[77]
- Initial data suggest that immunosuppressed patients are not at increased risk of severe illness from coronaviruses; however, further research is required on this patient group.[78]

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.[79]

Weak

smoking

- Early data on smoking as a risk factor for severe illness appear to be conflicting. Preliminary results from a meta-analysis found that active smoking is not significantly associated with an increased risk of severe disease.[80] However, a systematic review found that smoking is likely associated with negative progression and adverse outcomes.[81] Further research is warranted.

History & examination factors

Key diagnostic factors

fever (common)

- Reported in 83% to 98% of patients in case series.[20] [21] [37] [109] [110] [136] In one case series, 44% of patients had a fever on presentation, but it developed in 89% of patients after hospitalisation.[108]
- Children may not present with fever, or may have a brief and rapidly resolving fever.[12] [115] [116]
- 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.[20] [21] [37] [108] [109] [110] [136]
- Less common in children.[115]
- Cough is usually dry.

dyspnoea (common)

- Reported in 18% to 55% of patients in case series.[20] [21] [37] [108] [110] [136]
- Median time from onset of symptoms to development of dyspnoea is 5 to 8 days.[20] [21] [37]
- Polypnoea has been reported in children with severe illness.[118]

Other diagnostic factors

fatigue (common)

- Reported in 29% to 69% of patients in case series.[20] [37] [108] [110] [136]
- Patients may also report malaise.

myalgia (common)

- Reported in 11% to 44% of patients in case series.[20] [21] [37] [108] [109] [136]

anorexia (common)

- Reported in 40% of patients in case series.[37]

sputum production/expectoration (common)

- Reported in 26% to 33% of patients in case series.[20] [37] [108] [136]

sore throat (common)

- Reported in 5% to 17% of patients in case series, and usually presents early in the clinical course.[21] [37] [108] [136]
- Children may have pharyngeal erythema.[115]

confusion (uncommon)

- Reported in 9% of patients in case series.[21]

dizziness (uncommon)

- Reported in 9% to 12% of patients in case series.[37] [110]

headache (uncommon)

- Reported in 6% to 14% of patients in case series.[20] [21] [37] [108] [110] [136]

gastrointestinal symptoms (uncommon)

- Nausea, vomiting, abdominal pain, and diarrhoea have been reported in 1% to 11% of patients in case series, although this may be underestimated.[20] [21] [37] [108] [110] [136] [137] One case series reported gastrointestinal symptoms in nearly 40% of patients.[138]
- Some patients may present with predominantly gastrointestinal symptoms, especially children.[119] [120] [139]
- Patients may present with nausea or diarrhoea 1 to 2 days prior to onset of fever and breathing difficulties.[37]

haemoptysis (uncommon)

- Reported in 1% to 5% of patients in case series.[20] [108]

rhinorrhoea (uncommon)

- Reported in 4% to 5% of patients in case series.[21] [108]

chest pain (uncommon)

- Reported in 2% to 5% of patients in case series.[20] [21]
- May indicate pneumonia.

conjunctival congestion (uncommon)

- Reported in <1% of patients in case series.[108]

anosmia/dysgeusia (uncommon)

- There is anecdotal evidence that patients with mild illness may develop anosmia/hyposmia or ageusia/dysgeusia as an early symptom and in the absence of other symptoms. In one small cross-sectional survey in Italy, approximately 53% of hospitalised patients reported at least one taste or olfactory

disorder (or both).[140] It is possible that these patients may be hidden carriers, but further research is required.[141]

- 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).[142]

cutaneous manifestations (uncommon)

- Cutaneous manifestations (e.g., erythematous rash, petechiae, urticaria, vesicles) have been reported in some patients; however, further data is required to better understand skin involvement.[143] [144]

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 • Order in patients with severe illness. • Recommended in patients with respiratory distress and cyanosis.	**may show low oxygen saturation (SpO_2 <90%)**
ABG • Order in patients with severe illness as indicated to detect hypercarbia or acidosis. • Recommended in patients with respiratory distress and cyanosis who have low oxygen saturation (SpO_2 <90%).	**may show low partial oxygen pressure**
FBC • Order in patients with severe illness. • The most common laboratory abnormalities in patients hospitalised with pneumonia include leukopenia, lymphopenia, and leukocytosis. Other abnormalities include neutrophilia, thrombocytopenia, and decreased haemoglobin.[20] [21] [37] [122] • Thrombocytopenia has been associated with increased risk of severe disease and mortality and may be useful as a clinical indicator for monitoring disease progression.[145]	**leukopenia; lymphopenia; leukocytosis**
coagulation screen • Order in patients with severe illness. • The most common abnormalities are elevated D-dimer and prolonged prothrombin time.[20] [21] [37] • Non-survivors had significantly higher D-dimer levels and longer prothrombin time and activated partial thromboplastin time compared with survivors in one study.[146]	**elevated D-dimer; prolonged prothrombin time**
comprehensive metabolic panel • Order in patients with severe illness. • The most common laboratory abnormalities in patients hospitalised with pneumonia include elevated liver transaminases. Other abnormalities include decreased albumin and renal impairment.[20] [21] • Liver function abnormalities may be more common in patients with COVID-19 compared with other types of pneumonia.[132]	**elevated liver transaminases; decreased albumin; renal impairment**
serum procalcitonin • Order in patients with severe illness. • May be elevated in patients with secondary bacterial infection.[20] [21] May be more common in children.[121]	**may be elevated**
serum C-reactive protein • Order in patients with severe illness. • May be elevated in patients with secondary bacterial infection.[20] [21]	**may be elevated**
serum lactate dehydrogenase • Order in patients with severe illness. • Elevated lactate dehydrogenase has been reported in 73% to 76% of patients.[20] [21] May be more common in patients with COVID-19 compared with other types of pneumonia.[132]	**may be elevated**

Test	Result
• Indicates liver injury or lysis of blood erythrocytes.	
serum creatine kinase • Order in patients with severe illness. • Elevated creatine kinase has been reported in 13% to 33% of patients.[20] [21] • Indicates muscle or myocardium injury.	**may be elevated**
serum troponin level • Order in patients with severe illness. • May be elevated in patients with cardiac injury.[20]	**may be elevated**
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.[5] • Specimens should be collected prior to starting empirical antimicrobials if possible.	**negative for bacterial infection**
real-time reverse transcription polymerase chain reaction (RT-PCR) • Molecular testing is required to confirm the diagnosis. Nucleic acid sequencing may be required to confirm the diagnosis.[123] Priorities for testing depend on local guidelines and available resources. • 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.[123] • 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.[123] • Many tests are available under the US Food and Drug Administration's emergency-use authorisation scheme.[147] A point-of-care test that provides results within hours has been approved and will be available soon.[148] 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. • 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.[5] [125]	**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**
chest x-ray • Order 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.[20] [21] [128]	**unilateral or bilateral lung infiltrates**
computed tomography (CT) chest • Consider a CT scan of the chest. Abnormal chest CT findings have been reported in up to 97% of patients in one meta-analysis of	**bilateral ground-glass opacity or consolidation**

Test	Result
50,466 hospitalised patients.[109] CT is the primary imaging modality in China.[129] • CT imaging generally shows bilateral multiple lobular and subsegmental areas of ground-glass opacity or consolidation 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. Other atypical features include interlobular or septal thickening (smooth or irregular), thickening of the adjacent pleura, subpleural involvement, crazy paving pattern, and air bronchograms. 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. None of these findings appear to be specific or diagnostic for COVID-19.[20] [111] [130] 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.[131] 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.[130] 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.[132] • Small nodular ground-glass opacities are the most common finding in children.[133] Consolidation with surrounding halo signs is a typical finding in children.[121] • Evidence of viral pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[126] However, CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients.[47] [131] • 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.[135] [Fig-2]	

Emerging tests

Test	Result
serology • Serological testing is not available as yet, but assays are in development.[126] Serum samples can be stored to retrospectively define cases when validated serology tests become available. • Early data indicate continuous high levels of IgM during the acute phase of infection, with IgM lasting more than 1 month (indicating prolonged virus replication in infected patients). IgG responded later than IgM.[127]	**positive for SARS-CoV-2 virus antibodies**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Middle East respiratory syndrome (MERS)	• Lack of travel history to mainland China or other affected areas, or of close contact with an infected person in the 14 days prior to symptom onset. • Initial reports suggest that the clinical course of COVID-19 is less severe and the case fatality rate is lower compared with MERS (approximately 2% to 3% for COVID-19 versus 37% for MERS); however, there are no data to confirm this and the situation is rapidly evolving.[149] • Gastrointestinal symptoms and upper respiratory tract symptoms appear to be less common in COVID-19 based on early data.[149] [150]	• 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. • Lack of travel history to mainland China or other affected areas, or of close contact with an infected person in the 14 days prior to symptom onset. • Initial reports suggest that the clinical course of COVID-19 is less severe and the case fatality rate is lower compared with SARS (approximately 2% to 3% for COVID-19 versus 10% for SARS); however, there are no data to confirm this and the situation is rapidly evolving.[149] • Gastrointestinal symptoms and upper respiratory tract symptoms appear to be less common in COVID-19 based on early data.[149] [150]	• RT-PCR: positive for SARS-CoV viral RNA.
Community-acquired pneumonia	• Lack of travel history to mainland China or other affected areas, or of close contact with an infected	• Blood or sputum culture or molecular testing: positive for causative organism.

Condition	Differentiating signs / symptoms	Differentiating tests
	person in the 14 days prior to symptom onset. • Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.	
Influenza infection	• Lack of travel history to mainland China or other affected areas, or of close contact with an infected person in the 14 days prior to symptom onset. • Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. However, early reports suggest that sore throat is less common in COVID-19.[150]	• RT-PCR: positive for influenza A or B viral RNA.
Common cold	• Lack of travel history to mainland China or other affected areas, or of close contact with an infected person in the 14 days prior to symptom onset. • Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. However, early reports suggest that coryza and sore throat are less common in COVID-19.[150]	• RT-PCR: positive for causative organism, or negative for SARS-CoV-2 viral RNA.
Avian influenza A (H7N9) virus infection	• May be difficult to differentiate based on epidemiological history as avian influenza H7N9 is endemic in China. • 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. • Early reports suggest that sore throat is less common in COVID-19.[150]	• RT-PCR: positive for H7-specific viral RNA.
Avian influenza A (H5N1) virus infection	• Lack of travel history to mainland China or other affected areas, or of close	• RT-PCR: positive for H5N1 viral RNA.

Condition	Differentiating signs / symptoms	Differentiating tests
	contact with an infected person in the 14 days prior to symptom onset. • Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area when avian influenza is endemic. • Early reports suggest that sore throat is less common in COVID-19.[150]	
Other viral or bacterial respiratory infections	• Lack of travel history to mainland China or other affected areas, or of close contact with an infected person in the 14 days prior to symptom onset. • Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. • Adenovirus and *Mycoplasma* should be considered in clusters of pneumonia patients, especially in closed settings such as military camps and schools.	• Blood or sputum culture of molecular testing: positive for causative organism.
Pulmonary tuberculosis	• Consider diagnosis in endemic areas, especially in patients who are immunocompromised. • History of symptoms is usually longer. • Presence of night sweats and weight loss may help to differentiate.	• Chest x-ray: fibronodular opacities in upper lobes with or without cavitation; atypical pattern includes opacities in middle or lower lobes, or hilar or paratracheal lymphadenopathy, and/or pleural effusion. • Sputum acid-fast bacilli smear and sputum culture: positive. • Molecular testing: positive for *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.[151] • Symptoms of COVID-19 and neutropenic sepsis may be	• CBC: neutropenia.

Condition	Differentiating signs / symptoms	Differentiating tests
	difficult to differentiate at initial presentation.	

Diagnostic criteria

World Health Organization: case definitions[152]

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 human infection with coronavirus disease (COVID-19)]

Centers for Disease Control and Prevention: criteria to guide evaluation and laboratory testing for COVID-19[153]

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[154]

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.

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 international guidance on this issue as yet.[158] [159] [160]

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. Implement appropriate infection prevention and control procedures. COVID-19 is a notifiable disease; report all suspected and confirmed cases to your local health authorities.

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 for optimizing the supply of PPE]

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.[161] Guidance on when to stop isolation depends on local circumstances and may differ between countries; consult local guidelines.

Severe COVID-19

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 present with severe illness requiring oxygen therapy, and 5% present with critical illness requiring intensive care unit treatment.[9] The median time from onset of symptoms to hospital admission is reported to be approximately 7 days.[20] [37]

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]
- Discuss the risks, benefits, and potential outcomes of available treatment options with patients and their families using decision support tools where available. Take patient wishes and expectations into account when considering the ceiling of treatment.
- 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.[162]

Supportive therapies

- Oxygen and airway management: 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%.[5] [163] Titrate flow rates to reach a target SpO_2 ≥94% during resuscitation.[5] 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.[5] Some guidelines recommend that SpO_2 should be maintained no higher than 96%.[163]
- 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.[5]
- Prevention of complications: implement standard interventions to prevent complications associated with critical illness.[5] 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.

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.[5]
- Some patients with severe illness may require continued antimicrobial therapy once COVID-19 has been confirmed depending on the clinical circumstances.

Antipyretic/analgesic

- Guidelines recommend an antipyretic/analgesic for the relief of fever and pain.[5] [163] However, current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections.[164]
- 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.[165] There is currently no strong evidence to support this. The European Medicines Agency, the US Food and Drug Administration, and the WHO do not recommend avoiding NSAIDs in COVID-19 when clinically indicated. However, NHS UK recommends paracetamol as the drug of choice until there is more information available.[166] [167] [168]
- Ibuprofen is not recommended in pregnant women (especially in the third trimester) or children <3 months of age (age cut-offs vary by country).

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.[5]

Advanced oxygen/ventilatory support

- Follow local infection prevention and control procedures to prevent transmission to healthcare workers, especially when performing aerosol-generating procedures.
- Provide advanced oxygen/ventilatory support in patients who are deteriorating and failing to respond to standard oxygen therapy.[5] Some patients may develop severe hypoxic respiratory failure, requiring a high fraction of inspired oxygen, and high air flow rates to match inspiratory flow demand. Patients may also have increased work of breathing, demanding positive pressure breathing assistance.
- Consider a trial of high-flow nasal oxygen, or non-invasive ventilation if high-flow nasal oxygen is not available, in patients with hypoxaemic respiratory failure.[5] [163] Monitor patients closely for clinical deterioration that could result in the need for urgent intubation.[5] This procedure may avoid the need for intubation and mechanical ventilation.[169]
- Consider intubation and mechanical ventilation in patients who are acutely deteriorating. Two-thirds of patients who required critical care in the UK had mechanical ventilation within 24 hours of admission.[170] Endotracheal intubation should be performed by an experienced provider using airborne precautions. Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require pre-oxygenation with 100% fraction of inspired oxygen (FiO_2) for 5 minutes. Mechanically ventilated patients with acute respiratory distress syndrome 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.[5] [163]
- Consider prone ventilation in patients with persistent severe hypoxic failure.[5] [171] Pregnant women may benefit from being placed in the lateral decubitus position.[5] 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.[172]
- A trial of an inhaled pulmonary vasodilator may be considered in adults who have severe acute respiratory distress syndrome and hypoxaemia despite optimising ventilation. Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[163]
- Some patients may require extracorporeal membrane oxygenation (ECMO) according to availability and expertise.[5] [163] [173]
- The risk of treatment failure is high in patients with non-acutely reversible conditions, and there is also concern about nosocomial transmission with open ventilation systems and suboptimal non-invasive face mask or nasal pillow seals. More research to define the balance of benefits and risks to patients and health workers is needed.
- [Surviving Sepsis Campaign: summary of recommendations on the management of patients with COVID-19 and ARDS]
- [Surviving Sepsis Campaign: summary of recommendations on the initial management of hypoxic COVID-19 patients]

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.[5] See our Emerging section for more information about these treatments.

Corticosteroids

- Corticosteroids are being used in some patients with COVID-19; however, they have been found to be ineffective and are not recommended.[20] [174]
- 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.[5] However, 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.[163]
- A randomised controlled trial investigating the use of corticosteroids in patients with COVID-19 is in progress.[175]

Mild COVID-19 with risk factors

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.[155] 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.[155]

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.[155]

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 such as an antipyretic/analgesic (taking the precautions above into account), and advise patients to keep hydrated but not to take too much fluid as this can worsen oxygenation.

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.[155] 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 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.[5] [176]

Location of care

- Manage symptomatic pregnant women with confirmed infection in a hospital setting with appropriate maternal and fetal monitoring; women with severe illness or complications may require admission to an intensive care unit.[177]
- Isolate and monitor asymptomatic pregnant women with confirmed infection at home, if appropriate, with ultrasound fetal surveillance every 2 weeks.[177]

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).[5] [177]
- Corticosteroid therapy may be considered in women who are at risk of preterm birth from 24 to 37 weeks' gestation for fetal lung maturation.[5] [177] [178]

Newborns and breastfeeding

- Babies born to mothers with suspected or confirmed infection should be tested after birth.
- 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).[5] However, the CDC recommends that temporary separation of the mother and baby should be considered on a case-by-case basis, 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.[179] Consult local guidelines for specific recommendations.

Management of comorbidities

Data on the management of comorbidities in patients with COVID-19 is limited.[180] 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).[5]

Cardiovascular disease

- There is insufficient clinical or scientific evidence to determine how to manage hypertension in patients with COVID-19. There have been advocates for both the use and cessation of ACE inhibitors or angiotensin-II receptor antagonists in patients with hypertension due to theoretical concerns of increased expression of ACE2 in these patients.[181] However, the American Heart Association, the American College of Cardiology, the Heart Failure Society of America, and the European Society of Cardiology Council on Hypertension recommend that patients with COVID-19 who have underlying hypertension, heart failure, or ischaemic heart disease should continue taking their ACE inhibitors or angiotensin-II receptor antagonists as there is no evidence to suggest that these drugs increase the risk of developing severe COVID-19. In patients with cardiovascular disease who are diagnosed with COVID-19, individualised treatment decisions should be made according to the haemodynamic status and clinical presentation of each patient.[182] [183] [184] [185] The European Medicines Agency agrees with these recommendations.[186]
- [Centre for Evidence-Based Medicine: angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers in COVID-19]

Asthma

- There is currently no evidence of a relationship between the use of inhaled corticosteroids and COVID-19, and these agents are still considered safe to use. However, there is some evidence that inhaled corticosteroids may increase the risk of some respiratory infections in patients with asthma, and there is uncertainty over whether higher doses increase the risk of pneumonia.[187]

Cancer

- In patients who require systemic anticancer treatment, take into account: the level of immunosuppression associated with cancer types and individual treatments, as well as any other patient-specific factors; resource issues; and balancing the risk of not treating cancer optimally versus the risk of the patient being immunosuppressed and becoming severely ill from COVID-19.[151] Guidelines are also available for patients undergoing radiotherapy.[188]

Chronic kidney disease

- The impact of COVID-19 on chronic kidney disease has not been reported as yet; however, there are challenges for patients with suspected or confirmed COVID-19 infection who are on dialysis. Guidelines for patients on dialysis and for dialysis units have been developed.[189] [190] [191] [192] [193]

Inflammatory bowel disease

- There is a lack of data about COVID-19 in patients with inflammatory bowel disease; however, guidelines have been developed. Patients who are already on treatment should continue their current drug regimen if their disease is stable, and contact their healthcare provider to discuss suitable options during disease flares.[194] [195] [196]
- It has been suggested that patients should be screened for SARS-CoV-2 infection before starting therapy with biologics.[197]

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/analgesic

Acute (summary)

confirmed COVID-19

severe illness; mild illness with risk factors	1st	hospital admission
	plus	infection prevention and control procedures
	plus	assess adults for frailty
	plus	monitoring
	adjunct	supportive care
	adjunct	empirical antimicrobials
	adjunct	antipyretic/analgesic
	adjunct	advanced oxygen/ventilatory support
	adjunct	tailor management to comorbidities
	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/analgesic

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. 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.[5] [177]

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.[5]

» Consider treatment with a neuraminidase inhibitor until influenza is ruled out.[5]

» 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

Initial

start general supportive care interventions as indicated (e.g., haemodialysis, vasopressor therapy, fluid resuscitation, ventilation, antimicrobials) as appropriate.[5]

adjunct **supportive care**

Treatment recommended for SOME patients in selected patient group

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

» Oxygen and airway management: 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%.[5] [163] 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.[5] Some guidelines recommend that SpO_2 should be maintained no higher than 96%.[163]

» 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.[5]

adjunct **antipyretic/analgesic**

Treatment recommended for SOME patients in selected patient group

Primary options

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

OR

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

» Guidelines recommend an antipyretic/analgesic for the relief of fever and pain.[5] [163] However, current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections.[164]

Initial

» 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.[165] There is currently no strong evidence to support this. The European Medicines Agency, the Food and Drug Administration, and the WHO do not recommend avoiding NSAIDs in COVID-19 when clinically indicated. However, NHS UK recommends paracetamol as the drug of choice until there is more information available.[166] [167] [168]

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

Acute

confirmed COVID-19

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.[5]

» 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.[155]

» Symptomatic pregnant women with confirmed infection should be managed in a hospital setting with appropriate maternal and fetal monitoring; women with severe illness or complications may require admission to an intensive care unit.[177] 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.[5] [177]

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. 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]

» 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.[161] Guidance on when to stop isolation depends on local circumstances and may differ between countries; consult local guidelines.

plus **assess adults for frailty**

Acute

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. [Clinical frailty scale]

» Discuss the risks, benefits, and potential outcomes of available treatment options with patients and their families using decision support tools where available. Involve critical care teams in discussions about admission to critical care.[162]

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.[5]

adjunct **supportive care**

Treatment recommended for SOME patients in selected patient group

» Immediately start supportive care, if necessary.

» Oxygen and airway management: 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%.[5] [163] 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.[5] Some guidelines recommend that SpO_2 should be maintained no higher than 96%.[163]

» 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.[5]

» Implement standard interventions to prevent complications associated with critical illness.[5]

adjunct **empirical antimicrobials**

Acute

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/analgesic**

Treatment recommended for SOME patients in selected patient group

Primary options

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

OR

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

» Guidelines recommend an antipyretic/analgesic for the relief of fever and pain.[5] [163] However, current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections.[164]

» 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.[165] There is currently no strong evidence to support this. The European Medicines Agency, the Food and Drug Administration, and the WHO do not recommend avoiding NSAIDs in COVID-19 when clinically indicated. However, NHS UK recommends paracetamol as the drug of choice until there is more information available.[166] [167] [168]

» 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 **advanced oxygen/ventilatory support**

Treatment recommended for SOME patients in selected patient group

» Provide advanced oxygen/ventilatory support in patients who are deteriorating and failing to respond to standard oxygen therapy.[5] Follow

Acute

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 if high-flow nasal oxygen is not available, in patients with hypoxaemic respiratory failure.[5] [163] Monitor patients closely for clinical deterioration that could result in the need for urgent intubation.[5] This procedure may avoid the need for intubation and mechanical ventilation.[169]

» Consider intubation and mechanical ventilation in patients who are acutely deteriorating.[5] Endotracheal intubation should be performed by an experienced provider using airborne precautions. Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require pre-oxygenation with 100% fraction of inspired oxygen (FiO_2) for 5 minutes.[5] Mechanically ventilated patients with acute respiratory distress syndrome 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.[5] [163]

» Consider prone ventilation in patients with persistent severe hypoxic failure.[5] [163] Pregnant women may benefit from being placed in the lateral decubitus position.[5] 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.[172]

» A trial of an inhaled pulmonary vasodilator may be considered in adults who have severe acute respiratory distress syndrome and hypoxaemia despite optimising ventilation. Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[163]

» Some patients may require extracorporeal membrane oxygenation (ECMO) according to availability and expertise.[5] [163]

» The risk of treatment failure is high in patients with non-acutely reversible conditions, and there is also concern about nosocomial transmission with open ventilation systems and suboptimal non-invasive face mask or nasal pillow seals.

Acute

More research to define the balance of benefits and risks to patients and health workers is needed.

» [Surviving Sepsis Campaign: summary of recommendations on the management of patients with COVID-19 and ARDS]

» [Surviving Sepsis Campaign: summary of recommendations on the initial management of hypoxic COVID-19 patients]

adjunct **tailor management to comorbidities**

Treatment recommended for SOME patients in selected patient group

» 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).[5]

» Cardiovascular disease: there is insufficient clinical or scientific evidence to determine how to manage hypertension in patients with COVID-19. There have been advocates for both the use and cessation of ACE inhibitors or angiotensin-II receptor antagonists in patients with hypertension due to theoretical concerns of increased expression of ACE2 in these patients.[181] However, the American Heart Association, the American College of Cardiology, the Heart Failure Society of America, and the European Society of Cardiology Council on Hypertension recommend that patients with COVID-19 who have underlying hypertension, heart failure, or ischaemic heart disease should continue taking their ACE inhibitors or angiotensin-II receptor antagonists as there is no evidence to suggest that these drugs increase the risk of developing severe COVID-19. In patients with cardiovascular disease who are diagnosed with COVID-19, individualised treatment decisions should be made according to the haemodynamic status and clinical presentation of each patient.[182] [183] [184] [185] The European Medicines Agency agrees with these recommendations.[186] [Centre for Evidence-Based Medicine: angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers in COVID-19]

» Asthma: there is currently no evidence of a relationship between the use of inhaled corticosteroids and COVID-19, and these agents are still considered safe to use. However, there is some evidence that inhaled corticosteroids may increase the risk of some respiratory infections

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in patients with asthma, and there is uncertainty over whether higher doses increase the risk of pneumonia.[187]

» Cancer: in patients who require systemic anticancer treatment, take into account the following: the level of immunosuppression associated with cancer types and individual treatments, as well as any other patient-specific factors; resource issues; and balancing the risk of not treating cancer optimally versus the risk of the patient being immunosuppressed and becoming severely ill from COVID-19.[151] Guidelines are also available for patients undergoing radiotherapy.[188]

» Chronic kidney disease: the impact of COVID-19 on chronic kidney disease has not been reported as yet; however, there are challenges for patients with suspected or confirmed COVID-19 infection who are on dialysis. Guidelines for patients on dialysis and for dialysis units have been developed.[189] [190] [191] [192] [193]

» Inflammatory bowel disease: there is a lack of data about COVID-19 in patients with inflammatory bowel disease; however, guidelines have been developed. Patients who are already on treatment should continue their current drug regimen if their disease is stable, and contact their healthcare provider to discuss suitable options during disease flares.[194] [195] [196] It has been suggested that patients should be screened for SARS-CoV-2 infection before starting therapy with biologics.[197]

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.[5] See the Emergency 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

Acute

from local health authorities and available resources.[155] 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.[155]

» Asymptomatic pregnant women with confirmed infection can be managed at home, if appropriate.[177]

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

» 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.[155] 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.[177]

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.[155]

Acute

adjunct **antipyretic/analgesic**

Treatment recommended for SOME patients in selected patient group

Primary options

» paracetamol: children: consult local drug formulary for guidance on dose; adults: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day
» 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/analgesic for the relief of fever and pain.[5] However, current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections.[164]

» 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.[165] There is currently no strong evidence to support this. The European Medicines Agency, the Food and Drug Administration, and the WHO do not recommend avoiding NSAIDs in COVID-19 when clinically indicated. However, NHS UK recommends paracetamol as the drug of choice until there is more information available.[166] [167] [168]

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

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.[198] 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, and lopinavir/ritonavir are all potentially associated with an increased risk of cardiac death.[199] The World Health Organization and its partners have launched the Solidarity trial, a large international study to compare different treatments and ensure clear evidence of which treatments are most effective. The study will have five arms: standard of care; remdesivir; lopinavir/ritonavir; lopinavir/ritonavir plus interferon beta; and chloroquine.[200]

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.[201] [202] They are being trialled in patients for the treatment of mild to severe COVID-19.[203] [204] [205] They are also being trialled for prevention and post-exposure prophylaxis in the healthcare setting.[206] [207] Initial data is promising, but is currently limited to one study with considerable limitations. 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. The addition of azithromycin was thought to be synergistic.[208] Guidelines in China and Italy recommend these drugs for the treatment of COVID-19; however, this is based on weak evidence.[209] Hydroxychloroquine has similar therapeutic effects to chloroquine, but fewer adverse effects, is considered safe in pregnancy, and is more readily available in some countries.[210] Drug regulatory agencies have stressed that these drugs are not licensed to treat COVID-19, there is no evidence that they are safe and effective for the treatment of COVID-19, and they should only be used within the context of clinical trials. [Centre for Evidence-Based Medicine: chloroquine and hydroxychloroquine - current evidence for their effectiveness in treating COVID-19]

Remdesivir (GS-5734®)

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.[201] [211] [212] [213] [214] [215] [216] 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.[217] It appears to be safe to use in pregnancy.[176]

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.[218] 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.[219] It is considered safe in pregnancy.[176]

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.[220] 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.[221] [222] A small case series of five critically ill patients reported clinical improvement after treatment with convalescent plasma; however, this study had many limitations.[223] In the US, the Food and Drug Administration is also 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.[224]

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.[225]

Intravenous immunoglobulin

Intravenous immunoglobulin is being trialled in some patients with COVID-19; however, there are no data to support this.[21] [226]

Tocilizumab

An interleukin-6 receptor inhibiting monoclonal antibody that is currently approved for rheumatological conditions (e.g., rheumatoid arthritis, juvenile idiopathic arthritis) and cytokine release syndrome. Tocilizumab is being trialled in patients with severe COVID-19 to see whether it is effective in reducing the virus-induced cytokine storm, thereby potentially reducing complications.[227] [228] [229] [230] 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 tocilizumab (or any other anti-inflammatory drug) must be weighed against the possibly detrimental effects of impairment of immunity.[231]

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.[232] [233] [234]

Other treatments

Other drugs that may show promise for the treatment of COVID-19 include teicoplanin, camostat mesylate, Janus kinase inhibitors, sarilumab, gimsilumab, and leronlimab.[235] [236] [237] [238] [239] [240] Various other antiviral drugs (monotherapy and combination therapy) are being trialed in patients with COVID-19 (e.g., oseltamivir, darunavir, ganciclovir, favipiravir, baloxavir marboxil, umifenovir, ribavirin, interferon alfa, nebulised interferon beta).[241] [242] [243] [244] [245] [246] [247] [248] [249] Healthcare workers in Australia are trialling the Bacille Calmette-Guerin (BCG) vaccine.[250]

Traditional Chinese Medicine

Traditional Chinese Medicine is being trialled in some patients with COVID-19 (e.g., Xue-Bi-Jing, Shuang-Huang-Lian, Xin-Guan-2); however, there are no data to support this.[251] [252] [253] These medicines are commonly used in China to treat COVID-19 patients and are recommended in local guidelines.[254]

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.[5]

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.[177]

Perform molecular testing regularly during admission. Two consecutive negative tests (at least 24 hours apart) are required in a clinically recovered patient before discharge.[5]

Patient instructions

General prevention measures

- Wash hands often with soap and water or an alcohol-based hand sanitiser and 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]), particularly those who are sick.
- Stay at home if sick and isolate yourself from other people.
- Practice respiratory hygiene (i.e., cover mouth and nose when coughing or sneezing, discard tissue immediately in a closed bin, and wash hands).
- Regularly clean and disinfect frequently touched objects and surfaces.[82] [83]
- [WHO: coronavirus disease (COVID-19) advice for the public]

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 advice]
  - [Ministry of Manpower Singapore: advisories on COVID-19]

Pets

- Advise patients to limit their interaction, and avoid direct contact with their pets and other animals, especially while they are symptomatic. At this time, there is no evidence that pets and other animals can spread COVID-19; however, caution is advised.[288] [289]
- [CDC: animals and coronavirus disease 2019 (COVID-19)]

Resources

- [WHO: coronavirus disease (COVID-19) pandemic]
- [WHO: staying physically active during self-quarantine]
- [CDC: coronavirus (COVID-19)]
- [NHS UK: advice for everyone - coronavirus (COVID-19)]

Complications

Complications	Timeframe	Likelihood
acute respiratory distress syndrome (ARDS)	**short term**	**medium**
Reported in 15% to 33% of patients in case series.[20] [21] [37] [109] [136] Children can quickly progress to ARDS.[15] Factors that increase the risk of developing ARDS and death include older age, neutrophilia, elevated lactate dehydrogenase level, and elevated D-dimer levels.[272]		
acute liver injury	**short term**	**medium**
Reported in 14% to 53% of patients in case series. Occurs more commonly in patients with severe disease.[273] Although data support a higher prevalence of abnormal aminotransferase levels in patients with severe illness, evidence suggests that clinically significant liver injury is uncommon.[274]		
cardiovascular complications	**short term**	**low**
COVID-19 is associated with a high inflammatory burden that can cause vascular inflammation, cardiac arrhythmias, and myocarditis.[275] Acute cardiac injury has been reported in 7% to 20% of patients in case series, and indicated by elevated cardiac biomarkers.[20] [37] [136] [276] Prevalence is high among patients who are severely or critically ill, and these patients 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.[277] [278] [279] Patients with underlying cardiovascular disease but without myocardial injury have a relatively favourable prognosis.[280] Generally presents in two ways: acute myocardial injury and dysfunction on presentation; and myocardial injury that develops as the severity of illness worsens.[279] Fulminant myocarditis has been reported.[263] Early corticosteroid therapy and immunoglobulin may be beneficial in these patients.[281] Cardiomyopathy has been reported in 33% of critically ill patients. It is unknown whether it is a direct cardiac complication of COVID-19 or due to overwhelming clinical illness.[261] Myopericarditis with systolic dysfunction has been reported in a patient without signs/symptoms of pneumonia 1 week after the resolution of upper respiratory tract symptoms, highlighting the need for strict monitoring of patients with a history of cardiovascular disease.[282] Infection may have longer-term implications for overall cardiovascular health; however, further research is required.[283]		
secondary infection	**short term**	**low**
Reported in 6% to 10% of patients in case series.[20] [136]		
acute respiratory failure	**short term**	**low**
Reported in 8% of patients in case series.[21] Leading cause of mortality in patients with COVID-19.[263]		

Complications	Timeframe	Likelihood
Children can quickly progress to respiratory failure.[15]		
acute kidney injury	**short term**	**low**
Reported in 3% to 8% of patients in case series.[20] [21] [136]		
septic shock	**short term**	**low**
Reported in 4% to 8% of patients in case series.[20] [21] [37] [136] A systemic inflammatory response syndrome (SIRS) can sometimes accompany viral sepsis. Elevations in inflammatory chemokines and cytokines have been reported in COVID-19 patients.[20] [284] 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.[163]		
disseminated intravascular coagulation	**short term**	**low**
Reported in 71% of non-survivors.[146] 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.[285]		
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 (2%), intrauterine growth restriction (10%), and preterm birth (39%) have been reported.[54] [55] [57] [176] [286]		
rhabdomyolysis	**short term**	**low**
Reported as a late complication in one case report.[287]		

Prognosis

Case fatality rate

The overall global case fatality rate is approximately 4.5% based on World Health Organization data as of 29 March 2020. Current case fatality rates vary between countries, for example:[255]

- Italy - 11%
- Iran - 7%
- Spain - 8%

- UK - 6%
- US - 1.5%
- Australia - 0.4%.

The overall case fatality rate 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).[9]

Estimates that take into account asymptomatic patients and mild cases who have not been tested put the case fatality rate in the total population at around 0.125%; however, this estimate does not take into account exceptional cases (e.g., the current situation in Italy).[256] The case fatality rate among people on board the Diamond Princess cruise ship, a unique situation where a more accurate assessment of the case fatality rate in a quarantined population can be made, was 0.99%. However, it should be noted that the rate in a younger, healthier population could be lower.[257]

It is important to note that estimated case fatality rates should be treated with extreme caution as the situation is evolving rapidly, and case fatality rates are often overestimated at the onset of outbreaks owing to increased case detection of patients with severe disease.[258] For example, at the start of the 2009 H1N1 influenza pandemic the case fatality rate varied from 0.1% to 5.1% depending on the country, but ended up being around 0.02%. Other factors that can affect case fatality rates include testing rates in each country, delays between symptom onset and death, and local factors (e.g., patient demographics, availability and quality of health care, other endemic diseases). For example, the case fatality rate in Italy may be higher than in other countries 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. The way COVID-19 related deaths are identified and reported in Italy may have also resulted in an overestimation of cases.[256] [259]

The overall case fatality rate appears to be less than that reported for severe acute respiratory syndrome coronavirus (SARS) (10%) and Middle East respiratory syndrome (MERS) (37%).[20] Despite the lower case fatality rate, COVID-19 has so far resulted in more deaths than both SARS and MERS combined.[260]

Case fatality rate according to age and presence of comorbidities

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 case fatality rate 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).[9]

In the US, the case fatality rate 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 case fatality rate 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.[261]

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.[262]

Children have a better prognosis than adults, and deaths have been extremely rare (2 deaths have been identified in children up until 18 March 2020).[11]

Causes of death

The leading cause of death in patients with COVID-19 is respiratory failure from acute respiratory distress syndrome.[263]

In one retrospective study of 113 deceased patients, older age, male sex, presence of chronic hypertension or other cardiovascular comorbidites (as well as indicators of cardiac injury), symptoms related to hypoxaemia, and multi-organ dysfunction were more frequent in deceased patients compared with those who

recovered.[264] Other characteristics found to be more frequent in deceased patients include leukocytosis, lymphopenia, and elevated C-reactive protein level, and presence of complications.[265]

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. Non-survivors were more likely to develop acute respiratory distress syndrome and require mechanical ventilation. Non-survivors were older (>65 years of age) and more likely to have chronic medical illnesses.[266]

Prognostic factors

Factors associated with disease progression and a poorer prognosis in one retrospective analysis of 78 patients in Wuhan City include older age, history of smoking, maximum body temperature on admission, respiratory failure, significantly decreased serum albumin level, and significantly elevated C-reactive protein.[267]

Thrombocytopenia has been associated with increased risk of severe disease and mortality and may be useful as a clinical indicator for monitoring disease progression.[145]

Other factors associated with a poor prognosis include higher Sequential Organ Failure Assessment (SOFA) score and a D-dimer level >1 microgram/L. Viral shedding continued until death in non-survivors.[74]

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.[268]

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.[269] [270]

Disease 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. Further research is required on these patients.[271]

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 2019 (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

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

Interim US guidance for risk assessment and public health management of persons with potential coronavirus disease 2019 (COVID-19) exposures: geographic risk and contacts of laboratory-confirmed cases

Published by: Centers for Disease Control and Prevention **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

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

Coronavirus (covid-19): latest news and resources

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

COVID-19

Published by: European Centre for Disease Prevention and Control **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 community, during home care, and in health care settings in the context of COVID-19

Published by: World Health Organization **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

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

Information for healthcare professionals

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 therapeutic options 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

Discontinuation of in-home isolation for immunocompromised persons with COVID-19 (interim guidance)

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

Discontinuation of home isolation for persons with COVID-19 (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

Interim considerations for infection prevention and control of coronavirus disease 2019 (COVID-19) in inpatient obstetric healthcare settings

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

COVID-19: resource center

Published by: Infectious Diseases Society of America **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. WHO: novel coronavirus (COVID-19) situation dashboard *(external link)*
3. WHO: coronavirus disease (COVID-2019) situation reports *(external link)*
4. CDC: coronavirus disease 2019 (COVID-19) – cases in US *(external link)*
5. CDC: locations with confirmed COVID-19 cases, by WHO region *(external link)*
6. GenBank *(external link)*
7. WHO: coronavirus disease (COVID-19) advice for the public *(external link)*
8. BMJ: facemasks for the prevention of infection in healthcare and community settings *(external link)*
9. Public Health England: guidance on shielding and protecting people defined on medical grounds as extremely vulnerable from COVID-19 *(external link)*
10. BMJ: covid-19 in primary care (UK) *(external link)*
11. BMJ: covid-19 a remote assessment in primary care *(external link)*
12. WHO: infection prevention and control during health care when COVID-19 is suspected *(external link)*
13. CDC: interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings *(external link)*
14. CDC: strategies for optimizing the supply of PPE *(external link)*
15. WHO: global surveillance for human infection with coronavirus disease (COVID-19) *(external link)*
16. CDC: evaluating and testing persons for coronavirus disease 2019 (COVID-19) *(external link)*
17. CDC: priorities for testing patients with suspected COVID-19 infection *(external link)*
18. IDSA: COVID-19 prioritization of diagnostic testing *(external link)*
19. Clinical frailty scale *(external link)*
20. Surviving Sepsis Campaign: summary of recommendations on the management of patients with COVID-19 and ARDS *(external link)*
21. Surviving Sepsis Campaign: summary of recommendations on the initial management of hypoxic COVID-19 patients *(external link)*

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

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

24. Centre for Evidence-Based Medicine: angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers in COVID-19 *(external link)*

25. Centre for Evidence-Based Medicine: chloroquine and hydroxychloroquine - current evidence for their effectiveness in treating COVID-19 *(external link)*

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

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

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

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

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

31. Government of Canada: coronavirus disease (COVID-19) - travel advice *(external link)*

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

33. CDC: animals and coronavirus disease 2019 (COVID-19) *(external link)*

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

35. WHO: staying physically active during self-quarantine *(external link)*

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

37. NHS UK: advice for everyone - coronavirus (COVID-19) *(external link)*

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Images

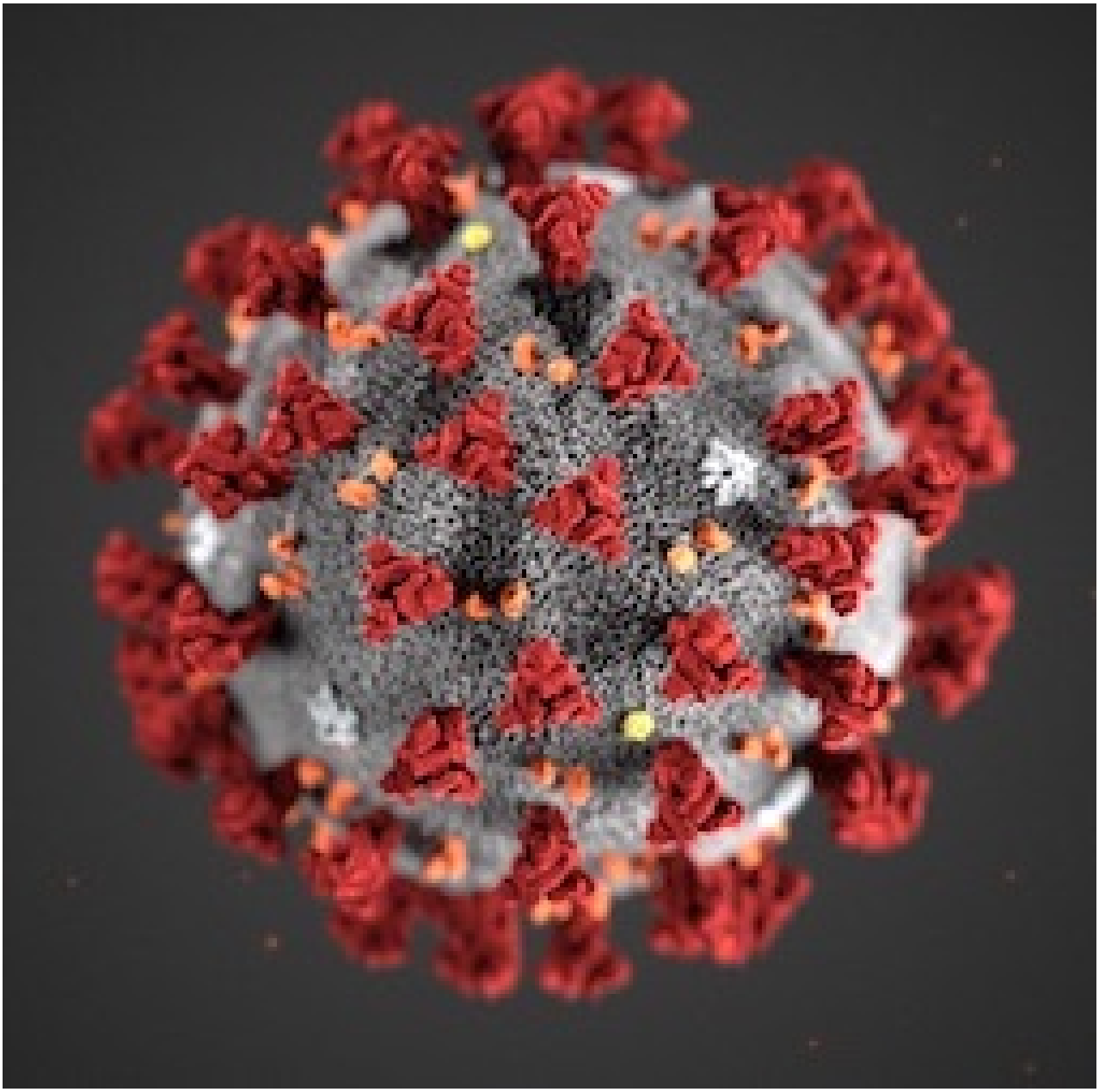

Figure 1: Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically

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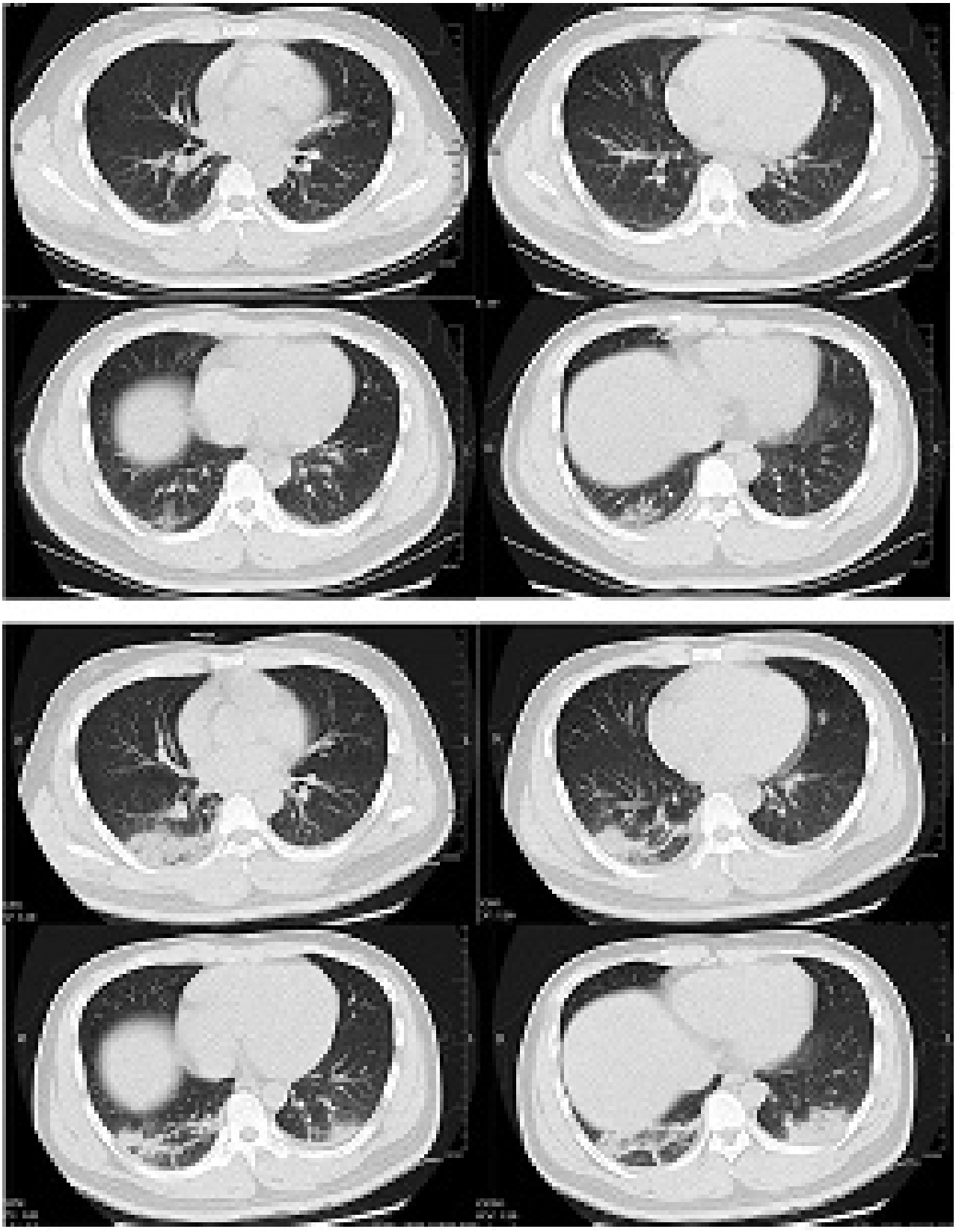

Figure 2: Transverse CT scans from a 32-year-old man, showing ground-glass opacity and consolidation of lower lobe of right lung near the pleura on day 1 after symptom onset (top panel), and bilateral ground-glass opacity and consolidation on day 7 after symptom onset

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