Coronavirus disease 2019 (COVID-19)

The right clinical information, right where it's needed
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The World Health Organization (WHO) was informed of cases of pneumonia of unknown microbial aetiology associated with Wuhan City, Hubei Province, China on 31 December 2019. The WHO later announced that a novel coronavirus had been detected in samples taken from these patients. Since then, the epidemic has escalated and rapidly spread around the world, with the WHO first declaring a public health emergency of international concern on 30 January 2020, and then formally declaring it a pandemic on 11 March 2020. Clinical trials and investigations to learn more about the virus, its origin, how it affects humans, and its management are ongoing.
Definition
A potentially severe acute respiratory infection caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The clinical presentation is generally that of a respiratory infection with a symptom severity ranging from a mild common cold-like illness, to a severe viral pneumonia leading to acute respiratory distress syndrome that is potentially fatal. Characteristic symptoms include fever, cough, and dyspnoea, although some patients may be asymptomatic. Complications of severe disease include, but are not limited to, multi-organ failure, septic shock, and blood clots.

Epidemiology

Adults

• In China, 87% of confirmed cases were aged 30 to 79 years and 3% were aged 80 years or older. Approximately 51% of patients were male.[4]
• In Italy, the median age and prevalence of comorbidities was higher compared with China.[5]
• In the UK, the median age of patients was 73 years and males accounted for 60% of admissions in a prospective observational cohort study of more than 20,000 hospitalised patients.[6]
• In the US, older patients (aged ≥65 years) accounted for 31% of all cases, 45% of hospitalisations, 53% of intensive care unit admissions, and 80% of deaths, with the highest incidence of severe outcomes in patients aged ≥85 years.[7]

Children

• Children are less likely to be affected than adults, and account for up to 5% of confirmed cases depending on geographical location:[4] [8] [9] [10] [11] [12] [13] [14] [15]
  • China: 2.1% (median age 7 years)
  • Italy: 1.2% (median age 4 to 5 years; higher in males but not statistically significant)
  • Spain: 0.8% (median age 3 years)
  • UK: <5% (increased risk in males)
  • US: 1.7% (median age 9.6 years or 17.3 years in critically ill; higher in males but not statistically significant).
• Most cases are from familial clusters, or children who have a history of close contact with an infected patient.[16] Unlike adults, children do not seem to be at higher risk for severe illness based on age or sex.[17]

Healthcare workers

• Infection rates in healthcare workers vary between countries. In the UK, 14% of healthcare workers who were screened tested positive.[18] In the Netherlands, 6% of healthcare workers who were tested were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[19] In China, infection rates in healthcare workers ranged from 1% to 4%.[20] [21]
• The majority of healthcare workers with COVID-19 reported contact in the healthcare setting. In a study of over 9000 cases reported in healthcare workers in the US, 55% had contact only in a healthcare setting, 27% only in a household, 13% only in the community, and 5% in more than one setting.[22]

Current case counts
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- [WHO: coronavirus disease (COVID-19) emergency dashboard]
- [WHO: coronavirus disease (COVID-2019) situation reports]
- [CDC: coronavirus disease 2019 (COVID-19) – cases in the US]
- [CDC: COVIDView]

**Aetiology**

**Virology**

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown betacoronavirus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019.[23]
- Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), and others that circulate among mammals and birds. Rarely, animal coronaviruses can spread to humans and subsequently spread between people, as was the case with SARS and MERS.
- SARS-CoV-2 belongs to the *Sarbecovirus* subgenus of the *Coronaviridae* family, and is the seventh coronavirus known to infect humans. The virus has been found to be similar to SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV.[24] [25] 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.[26]

**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.[27] [28] [29]
- 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.[24] [25] [30] [31] Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses.[32] [33] Nearly 5 months after the initial outbreak, the virus is yet to be identified in an animal host.[34]

**Transmission dynamics**

- Person-to-person spread has been confirmed in community and healthcare settings, with local transmission occurring in many countries around the world.
- An initial assessment of the transmission dynamics in the first 425 confirmed cases found that 55% of cases before 1 January 2020 were linked to the Huanan South China Seafood Market, whereas only 8.6% of cases after this date were linked to the market. This confirms that person-to-person spread...
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occurred among close contacts since the middle of December 2019, including infections in healthcare workers.[29]

• It is uncertain how easily the virus spreads between people, but transmission in chains involving several links has been recognised. Available evidence indicates that human transmission occurs via close contact with respiratory droplets produced when a person exhales, sneezes, or coughs; via direct contact with infected people; or, more rarely, via contact with fomites. Airborne transmission has not been reported or confirmed; however, it may be possible during aerosol-generating procedures performed in clinical care.[27] [29] [35] [36] [37]

• Preliminary reports suggested that the reproductive number (\(R_0\)), the number of people who acquire the infection from an infected person, was estimated to be 2.2 to 3.3.[29] [38] However, the \(R_0\) may actually be lower in light of social distancing measures that have been instituted.[39]

• 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).[40] In healthcare settings, the virus is widely distributed in the air and on object surfaces (e.g., floors, rubbish bins, sickbed handrails, and computer mice) in both general wards and intensive care units, with a greater risk of contamination in the intensive care unit.[41]

• The contribution to transmission by the presence of the virus in other body fluids is unknown; however, the virus has been detected in blood, cerebrospinal fluid, pericardial fluid, placental tissue, urine, saliva, tears, and conjunctival secretions. Faecal-oral transmission may be possible (virus has been detected in the stool samples of almost half of the patients in one meta-analysis), although it has not been reported yet.[42] [43] [44] [45] [46] [47] [48] [49] [50] Patients with diarrhoea are more likely to have viral RNA in their stool.[51] The presence of virus in these fluids or viral RNA shedding does not necessarily equate with infectivity. Although viral components have been detected in semen, it is unknown whether this demonstrates infectivity. Sexually transmitted infection has not yet been reported.[52] The virus has been detected in the breast milk of one mother; the significance of this is unknown.[53]

• Nosocomial transmission in healthcare workers and patients has been reported in 41% of patients in one case series.[54]

• Widespread transmission has been reported in long-term care facilities, homeless shelters, meat processing facilities, and prisons, and on cruise ships (19% of 3700 passengers and crew were infected aboard the Diamond Princess).[55] [56] [57] [58] [59] [60]

• Clusters of cases originating from family gatherings, weddings, choir practices, fitness classes, religious gatherings, and churches have been reported.[61] [62] [63] [64] [65] [66]

• The secondary attack rate among all close contacts is approximately 0.45% to 0.7%.[36] [67] The secondary attack rate among household members is higher and ranges from 4.6% to 30%.[36] [67] [68] [69] The secondary attack rate in children is lower compared with adults, and is higher for spouse contacts of the index case. The rate lowered to 0% in one study where index patients were quarantined by themselves from the onset of symptoms.[69]

Presymptomatic transmission

• The incubation period is estimated to be between 1 and 14 days, with a median of 4 to 7 days (may be shorter or longer in children). Approximately 97.5% of patients develop symptoms within 11.5 days of infection. A small number of studies suggest that some people can be contagious during the incubation period, the time between exposure to the virus and the onset of symptoms.[70] [71] [72] [73] [74] [75]
Coronavirus disease 2019 (COVID-19) Basics

• Presymptomatic transmission has been reported in 12.6% of cases in China.[76] A study in Singapore identified 6.4% of patients among seven clusters of cases in which presymptomatic transmission was likely to have occurred 1 to 3 days before symptom onset.[77]
• The overall secondary attack rate for close contacts of presymptomatic people is approximately 3.3%, with a rate of 16.1% for household contacts, 1.1% for social contacts, and 0% for work contacts.[78]
• Presymptomatic transmission still requires the virus to be spread by infectious droplets or contact with fomites.

Asymptomatic transmission

• An asymptomatic case is a laboratory-confirmed case who does not develop symptoms. There is some evidence that spread from asymptomatic carriers is possible, although it is thought that transmission is greatest when people are symptomatic (especially around the time of symptom onset).[79] [80] [81] [82] [83] [84] [85]
• 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.[86] However, a Japanese study of citizens evacuated from Wuhan City estimates the rate to be closer to 31%.[87] Early data from an isolated village of 3000 people in Italy estimates the figure to be higher at 50% to 75%.[88] Other studies ranged from 4% to 80%.[89]
• Data from a long-term care facility in the US found that 30% of patients with positive test results were asymptomatic (or presymptomatic) on the day of testing.[90] In a skilled nursing facility, 64% of residents tested positive 3 days after one resident tested positive; 56% of the residents who tested positive and participated in point-prevalence surveys were asymptomatic at the time of testing, although most went on to develop symptoms.[91]
• Asymptomatic (or paucisymptomatic) transmission has been reported in family clusters.[92]
• The proportion of asymptomatic cases in children is thought to be significant, and children may play a role in community spread.[93] However, there is a case report of an asymptomatic child who did not transmit the disease to 172 close contacts, despite close interactions within schools. This suggests that there may be different transmission dynamics in children.[94]

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.[95]
• 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.[96] [97]
• 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.[96]

Perinatal transmission

• It is unknown whether perinatal transmission (including transmission via breastfeeding) is possible. A meta-analysis found that there is currently no evidence of vertical transmission.[98] 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.[99] [100] [101] [102] [103]
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.[104][105] High viral load at baseline may be associated with more severe disease and risk of disease progression.[106]

- Pharyngeal viral shedding is high during the first week of symptoms when symptoms are mild or prodromal, peaking on day 4. This suggests active virus replication in upper respiratory tract tissues.[107]

- The median duration of viral shedding has been estimated to be between 8 and 20 days after symptoms resolve. However, the virus has been detected for up to 60 days in various samples. It is unclear whether the virus is capable of transmission later in the course of the disease.[108][109][110][111][112][113] When comparing viral shedding in symptomatic versus asymptomatic patients, duration of viral shedding was longer in symptomatic patients compared with asymptomatic patients (25.2 days versus 22.6 days).[114] Viral shedding continued until death in non-survivors.[108]

- Factors associated with prolonged viral shedding include male sex, older age, comorbid hypertension, delayed admission to hospital after symptom onset or severe illness on admission, and use of invasive mechanical ventilation or corticosteroids.[115]

- The duration of viral shedding is significantly longer in stool samples than in respiratory and serum samples. The median duration of viral shedding in stool samples was 22 days, compared with 18 days in respiratory samples and 16 days in serum samples. The median duration of shedding was lower in mild illness (14 days) compared with severe illness (21 days).[116]

Pathophysiology

The pathophysiology of COVID-19 is not fully understood; however, it has been confirmed that SARS-CoV-2 binds to the angiotensin-converting enzyme-2 (ACE2) receptor in humans, which suggests a similar pathogenesis to SARS.[25][117] 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.[118] 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.[119]

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.[120] This may explain the extrapulmonary manifestations associated with infection. Lower expression of ACE2 in the nasal epithelium of children ages <10 years compared with adults may explain why COVID-19 is less prevalent in children; however, further research on this is required.[121]

The virus uses the host transmembrane protease serine 2 (TMPRSS2) for S protein priming and fusion of viral and host cell membranes.[122] A furin-like cleavage site has been identified in the spike protein of the virus; this does not exist in other SARS-like coronaviruses.[123]

Autopsy studies have revealed that patients who died of respiratory failure had evidence of exudative diffuse alveolar damage with massive capillary congestion, often accompanied by microthrombi. Pulmonary artery
obstruction by thrombotic material at both the macroscopic and microscopic levels has been identified.
Patients also had signs of generalised thrombotic microangiopathy. Severe endothelial injury associated
with the presence of intracellular virus and disrupted cell membranes has been noted. Other findings include
bronchopneumonia, pulmonary embolism, alveolar haemorrhage, and vasculitis. Significant new blood
vessel growth through intussusceptive angiogenesis distinguishes the pulmonary pathology of COVID-19
from severe influenza infection.[124] [125] [126] [127]

There is a hypothesis that COVID-19 is a disease of the endothelium.[128] [129] [130] Hyperviscosity has
been reported in patients. It is known to damage the endothelium, and is a known risk factor for thrombosis.
The potential link between hyperviscosity and thrombotic complications warrants further investigation.[131]

Classification


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
  - $\text{SpO}_2 \leq 93\%$ on room air.

Severe pneumonia in children

- Cough or difficulty breathing plus at least one of the following:
  - Central cyanosis or $\text{SpO}_2 < 90\%$
  - 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 of age: ≥40 breaths/minute).
• While the diagnosis is made on clinical grounds, chest imaging may identify or exclude some pulmonary complications.

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

Asymptomatic or presymptomatic infection

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

Mild illness

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

Moderate illness

• People who have evidence of lower respiratory disease by clinical assessment or imaging and an oxygen saturation (SpO₂) >93% on room air at sea level.

Severe illness

• People who have respiratory frequency >30 breaths per minute, SpO₂ ≤93% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) <300, or lung infiltrates >50%.

Critical illness

• People who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Primary prevention

Infection prevention and control for healthcare professionals

- Immediately isolate all suspected cases in an area that is separate from other patients.[220]
- Implement standard precautions at all times:[220]
  - 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:[220]
  - Place patients in adequately ventilated single rooms; when single rooms are not available, place all suspected cases together in the same ward
  - Wear a medical mask, gloves, an appropriate gown, and eye/facial protection (e.g., goggles or a face shield)
  - Use single-use or disposable equipment
  - Consider limiting the number of healthcare workers, family members, and visitors in contact with the patient, ensuring optimal patient care and psychosocial support for the patient
  - Consider placing patients in negative pressure rooms, if available.

- Implement airborne precautions when performing aerosol-generating procedures. Some countries and organisations recommend airborne precautions for any situation involving the care of a COVID-19 patient.[220]
- All specimens collected for laboratory investigations should be regarded as potentially infectious.[220]
- It is important to clean and disinfect inanimate surfaces in the surgery or hospital. Follow local cleaning and disinfection procedures.[221]

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

Telehealth for primary care physicians

- It is important that primary care physicians avoid in-person assessment of patients with suspected COVID-19 in primary care when possible to avoid infection.[222] Most patients can be managed remotely by telephone or video consultations.[223] Algorithms for dealing with these patients are available:
  - [BMJ: covid-19 in primary care (UK)]
  - [BMJ: covid-19 - a remote assessment in primary care]

General prevention measures

- People should be advised to:[224] [225]
  - Wash hands often with soap and water for at least 20 seconds or an alcohol-based hand sanitiser (that contains at least 60% alcohol), especially after being in a public place, blowing
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coughing or sneezing. Avoid touching the eyes, nose, and mouth with unwashed hands

- Avoid close contact with people (i.e., maintain a distance of at least 1 metre [3 feet]) including shaking hands, particularly those who are sick, have a fever, or are coughing or sneezing. It is important to note that recommended distances differ between countries (for example, 2 metres is recommended in the US and UK) and you should consult local guidance. Avoid going to crowded places

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

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

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

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

Face masks

- Recommendations on the use of face masks in community settings vary between countries.[226] It is mandatory to wear a mask in public in certain countries, and masks may be worn in some countries according to local cultural habits. Consult local guidance for more information.

- The World Health Organization (WHO) recommends that medical masks should be reserved for healthcare workers. People with symptoms should also wear a medical mask, self-isolate, and seek medical advice as soon as possible. Masks are also recommended for those caring for a sick person at home when in the same room. There is currently no evidence that wearing a mask (medical or other types) in the community setting can prevent infection with respiratory viruses, including COVID-19, in a healthy person.[227]

- The Centers for Disease Control and Prevention recommends that homemade cloth face coverings can be worn in public settings where social distancing measures are difficult to maintain (e.g., pharmacies, supermarkets), especially in areas where there is significant community transmission.[228] However, there is no evidence to support this.[229]

- Use of a mask alone is insufficient to provide adequate protection, and they should be used in conjunction with other infection prevention and control measures such as frequent hand hygiene and social distancing. It is important to wash your hands with soap and water (or an alcohol-based sanitiser) prior to putting on a face mask, and to remove it correctly. Used masks should be disposed of properly.[227] [230]

- Standard surgical masks are as effective as respirator masks for preventing infection of healthcare workers in outbreaks of viral respiratory illnesses such as influenza, but it is unknown whether this applies to COVID-19.[231] A small study found that surgical and cotton masks are ineffective at preventing viral spread to the environment from the cough of patients with COVID-19.[232]

Screening and quarantine

- People travelling from areas with a high risk of infection may be screened using questionnaires about their travel, contact with ill persons, symptoms of infection, and/or measurement of their temperature. Combined screening of airline passengers on exit from an affected area and on arrival elsewhere has
been relatively ineffective when used for other infections such as Ebola virus infection, and has been modelled to miss up to 50% of cases of COVID-19, particularly those with no symptoms during the incubation period.[233] Symptom-based screening processes have been reported to be ineffective in detecting severe acute respiratory syndrome coronavirus 2 (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.[234]

- Enforced quarantine is being used to isolate easily identifiable cohorts of people at potential risk of recent exposure (e.g., groups evacuated by aeroplane from affected areas, people returning to their home countries before border closures, or groups on cruise ships with infected people on board).[235] The psychological effects of enforced quarantine may have long-lasting repercussions.[236] [237] Despite limited evidence, a Cochrane review found quarantine to be important in reducing the number of people infected and deaths, especially when started earlier and when used in combination with other prevention and control measures.[238]

Social distancing

- Many countries have implemented mandatory social distancing measures in order to reduce and delay transmission (e.g., city lockdowns, stay-at-home orders, curfews, non-essential business closures, bans on gatherings, school and university closures, travel restrictions and bans, remote working, quarantine of exposed people/travellers).
- Although the evidence for social distancing for COVID-19 is limited, it is emerging, and the best available evidence appears to support social distancing measures to reduce the transmission and delay spread. The timing and duration of these measures appears to be critical.[239] [240] Researchers in Singapore found that social distancing measures (isolation of infected individuals and family quarantine, school closures, and workplace distancing) significantly decreased the number of infections in simulation models.[241]
- [Public Health England: staying alert and safe (social distancing)]

Shielding extremely vulnerable people

- Shielding is a measure used to protect vulnerable people (including children) who are at very high risk of severe illness from COVID-19 because they have an underlying health condition. Shielding involves minimising all interactions between those who are extremely vulnerable and other people to protect them from coming into contact with the virus.
- Extremely vulnerable groups include:[169]
  - 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 that significantly increase the risk of infections (e.g., sickle cell anaemia, severe combined immunodeficiency)
  - People on immunosuppression therapies sufficient to significantly increase the risk of infection
  - Women who are pregnant with significant heart disease (congenital or acquired).
- These groups are advised to not leave their house, to not attend any gatherings (including gatherings of friends and family in private spaces), and to strictly avoid contact with someone who is displaying symptoms of COVID-19. The UK government is recommending that people shield until the end of June, and is regularly monitoring this position. Shielding is a personal decision and is not mandatory.
- Visits from people who provide essential support should continue provided these people do not have symptoms and follow hand hygiene measures.
- Consult local health authorities for more guidance as recommendations, procedures, and resources differ between countries.
- [Public Health England: guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19]
Vaccines

- There is currently no vaccine available. Vaccines are in development, but it may take at least 12 to 18 months before one is available. Several vaccine candidates are currently approved for human testing through clinical trials, including mRNA and DNA platform vaccines, adenovirus vector vaccines, and inactivated virus vaccines.[242]
- Previous trials of coronavirus vaccines identified cellular immunopathology and antibody-dependent enhancement (ADE) as potential safety issues, so there are concerns over ADE of SARS-CoV-2 due to prior exposure to other coronaviruses (such as those that cause the common cold).[243][244]
- Results from preliminary animal and human studies are beginning to emerge, but scientists urge caution over the results.[245]
- Ad5-nCoV: a recombinant adenovirus type-5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike glycoprotein. Results from a single-centre, open-label, non-randomised, dose-escalation phase 1 trial in China report that the vaccine was immunogenic, inducing humoral responses (peaking 28 days after vaccination) and T-cell responses (peaking 14 days after vaccination) in most participants. Participants were healthy and had no underlying diseases. At least one adverse reaction was reported within the first 7 days after vaccination in 83% (low- and medium-dose groups) and 75% (high-dose group) of participants. The most common adverse reactions reported included injection-site reactions, fever, fatigue, headache, and muscle pain. No serious adverse events were noted within 28 days of vaccination. A phase 2 trial is ongoing.[246]
- ChAdOx1 nCoV-19: an adenovirus vector vaccine that carries the SARS-CoV-2 spike protein. Preliminary results (not peer reviewed) from animal studies found that a single dose induced a humoral and cellular response in mice and rhesus macaques. However, while viral loads in bronchoalveolar lavage fluid and lung tissues of vaccinated animals were significantly reduced compared with unvaccinated animals, reduction in viral shedding from the nose was not observed.[247] Despite this, researchers are moving to human trials.
- Inactivated SARS-CoV-2 virus (Sinovac®): contains a more traditional chemically inactivated version of the virus. The vaccine was found to induce immunity in mice, rats, and non-human primates. When challenged with the virus, monkeys who were vaccinated with the highest dose of the vaccine did not develop infection, and no virus was recovered from the throat, lung, or rectum.[248]
- mRNA-1273: a novel vaccine that uses mRNA technology not previously approved for use in humans. The mRNA encodes for a full-length prefusion stabilised spike protein of SARS-CoV-2 and is encapsulated in a lipid nanoparticle. Animal studies in mice have been completed, but testing in other animals such as hamsters, ferrets, and non-human primates has been skipped in order to expedite the vaccine development process. Results from a phase 1 trial indicated that all 45 healthy adults (ages 18-55 years) seroconverted by day 15 after the first dose, according to a press release issued by the manufacturer. Of the cohort of 15 patients who received the highest dose (250 micrograms), 20% of participants experienced grade adverse events following the second dose (the press release does not say what these were). Of the two cohorts who received the 25 microgram and 100 microgram doses, only one patient experienced a grade 3 adverse event (erythema at injection site). No grade 4 adverse events were reported in this small cohort. The study did not include people with underlying conditions.[249] mRNA-1273 has been granted fast-track designation by the US Food and Drug Administration, and phase 2 trials are expected to start soon.

Immunity passports

- Some governments are discussing or implementing certifications for people who have contracted and recovered from COVID-19 based on antibody tests (sometimes called ‘immunity passports’). Possession of a passport would allow people to have a greater range of privileges (e.g., work, education, travel). However, the WHO does not support these certifications as there is currently no evidence that people who have recovered from infection and have antibodies are protected from reinfection.[250] Other potential issues include lack of public support for these measures, potential for discrimination of groups of people, testing errors (including cross-reactivity with other human coronaviruses), access to testing, fraud, legal and ethical objections, and people getting infected intentionally in order to obtain a certification.[251]
• Past or current smokers have nearly double the risk for severe disease, and smoking cessation should be encouraged.[165] The WHO recommends that tobacco users stop using tobacco given the well-established harms associated with tobacco use and second-hand smoke exposure.[167]

**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:[383]

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

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

**Screening of travellers**

Exit and entry screening may be recommended in countries where borders are still open, particularly when repatriating nationals from affected areas. Travellers returning from affected areas should self-monitor for symptoms for 14 days and follow local protocols of the receiving country. Some countries may require travellers to enter mandatory quarantine in a designated location (e.g., a hotel). Travellers who develop symptoms are advised to contact their local healthcare provider, preferably by phone.[384] One study of 566 repatriated Japanese nationals from Wuhan City found that symptom-based screening performed poorly and missed presymptomatic and asymptomatic cases. This highlights the need for testing and follow-up.[385]

**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.[386]
Case history

Case history #1

A 61-year-old man presents to hospital with fever, dry cough, and difficulty breathing. He also reports feeling very tired and unwell. He has a history of hypertension, which is controlled with enalapril. On examination, his pulse is 120 bpm, his temperature is 38.7°C (101.6°F), and his oxygen saturation is 88%. He appears acutely ill. He is admitted to hospital in an isolation room and is started on oxygen, intravenous fluids, and empirical antibiotics. Chest x-ray shows bilateral lung infiltrates, and computed tomography of the chest reveals multiple bilateral lobular and subsegmental areas of ground-glass opacity. A nasopharyngeal swab is sent for real-time reverse transcriptase polymerase chain reaction testing, and the result comes back positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) the next day. The patient develops respiratory distress 7 days after admission and is transferred to the intensive care unit and started on mechanical ventilation.

Case history #2

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

Step-by-step diagnostic approach

Early recognition and rapid diagnosis are essential to prevent transmission and provide supportive care in a timely manner. Have a high index of clinical suspicion for COVID-19 in all patients who present with fever and/or acute respiratory illness and who live in or report a travel history to an area with local transmission or close contact with a suspected or confirmed case in the 14 days prior to symptom onset. Triage all patients on admission and immediately isolate all suspected and confirmed cases in an area separate from other patients. Implement local infection prevention and control procedures. COVID-19 is a notifiable disease.

History

Take a detailed history to ascertain the level of risk for COVID-19 and assess the possibility of other causes, including a travel history and an assessment of risk factors.

Diagnosis should be suspected in:[132]

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

See Diagnostic criteria section for case definitions.
Clinical presentation in adults

Approximately 15% of patients present with the symptom triad of fever, cough, and dyspnoea, and 90% present with more than one symptom.[28] Some patients may be minimally symptomatic or asymptomatic, while others may present with severe pneumonia or complications such as acute respiratory syndrome, septic shock, acute myocardial infarction, venous thromboembolism, or multi-organ failure.

The most common symptoms are:[27] [28] [252] [75] [253] [254]

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

Less common symptoms include:

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

The clinical presentation has varied slightly across geographical locations. Initial impressions from the US note that the clinical presentation may be broader than that observed in China and Italy, with chest pain, headaches, altered mental status, and gastrointestinal symptoms all observed on initial presentation. Severe hepatic and renal dysfunction that spares the lungs has also been observed.[255] Data from the first hospitalised patients in New York found that while the most common presenting symptoms were fever, cough, dyspnoea, and myalgia, gastrointestinal symptoms appeared to be more common than in China.[138]

In terms of severity:[4]

- 80% present with mild illness
- 14% present with severe illness
- 5% present with critical illness.

The most prevalent symptoms in patients with mild to moderate illness, according to one European study, are headache, loss of smell, nasal congestion, cough, asthenia, myalgia, rhinorrhoea, gustatory dysfunction, and sore throat. Fever was reported less commonly. The mean duration of symptoms was 11.5 days. The presentation varied according to age, with younger patients generally having ear, nose, and throat complaints, and older patients generally having fever, fatigue, and loss of appetite.[256]

Pregnant women
• The clinical characteristics in pregnant women are similar to those reported for non-pregnant adults, and 78% of pregnant women have mild to moderate symptoms.**[98]** 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.**[2]**

Atypical presentations

• Atypical presentations may occur, especially in older patients (e.g., falls, delirium/confusion, functional decline, syncope, persistent hiccups) and patients who are immunocompromised (e.g., absence of fever). Older patients and those with comorbidities may present with mild symptoms, but have a high risk of deterioration.**[2]**

Co-infections

• Co-infections have been reported (most commonly influenza, rhinovirus/enterovirus, respiratory syncytial virus, and non-SARS-CoV-2 **Coronaviridae** as well as **Streptococcus pneumoniae** and **Mycoplasma pneumoniae** ) in between 1% and 10% of patients, and the risk is higher in patients in critical care. Co-infections may be associated with protracted respiratory symptoms, prolonged intensive care stay, morbidity, and mortality if not detected and treated early.**[211]** **[257]** **[258]** **[259]** **[260]** Patients with influenza co-infection showed similar clinical characteristics to patients with COVID-19 only.**[261]** **[262]**

Clinical presentation in children

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

Evidence so far suggests a milder, or asymptomatic, course of disease in about 95% of children, but with possible evidence of radiological lung changes in both categories. Symptoms commonly reported include fever, cough, sore throat, nasal congestion, and rhinorrhea. Dyspnoea is less common in children compared with adults. Children may present with gastrointestinal symptoms more commonly than adults, particularly newborns and infants, and they may be the only symptom.**[263]** Febrile seizures have been reported rarely.**[12]**

Severe disease has been reported rarely in children.**[263]** **[264]** In a cross-sectional study of 48 critically ill infants and children in the US, the clinical course and hospital outcomes were better compared with adults. Similar to adults, 80% of critically ill children had pre-existing comorbidities, most commonly immune suppression/cancer, obesity, and diabetes.**[265]** There is increasing concern that a related inflammatory syndrome is emerging in children with severe disease. See the Complications section for more information.

Cases of COVID-19 have been reported in neonates. Dyspnoea is the most common sign in neonates. Although illness is usually mild, severe illness, including cases of late-onset neonatal sepsis and encephalitis, has been reported. Severe illness is slightly more common in neonates compared with older children. Infants may present with irritability, crying, feeding difficulties, silent hypoxia, and neurological symptoms.**[263]** **[266]** **[267]** **[268]**

Co-infections may be more common in children.**[269]** Co-infection was documented in 6% of children in US and Italian studies, with the most common pathogens being respiratory syncytial virus, rhinoviruses,
Epstein-Barr virus, enteroviruses, influenza A, non-SARS coronaviruses, and *Streptococcus pneumoniae*.\[11\] \[12\]

**Physical examination**

Perform a physical examination. Avoid use of a stethoscope if possible due to risk of viral contamination. Patients may be febrile (with or without chills/rigors) and have obvious cough and/or difficulty breathing. Auscultation of the chest may reveal inspiratory crackles, rales, and/or bronchial breathing in patients with pneumonia or respiratory distress. Patients with respiratory distress may have tachycardia, tachypnoea, or cyanosis accompanying hypoxia.

**Pulse oximetry**

Pulse oximetry may reveal low oxygen saturation (SpO₂ <90%). Clinicians should be aware that patients with COVID-19 can develop ‘silent hypoxia’: their oxygen saturations can drop to low levels and precipitate acute respiratory failure without the presence of obvious symptoms of respiratory distress. Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognising further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.\[270\]

While NEWS2 is still recommended for use in patients with COVID-19, the UK Royal College of Physicians now advises that any increase in oxygen requirements in these patients should trigger an escalation call to a competent clinical decision maker, and prompt an initial increase in observations to at least hourly until a clinical review happens.\[271\]

**Initial laboratory investigations**

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

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

The most common laboratory abnormalities in patients hospitalised with pneumonia include lymphopenia, leukocytosis, thrombocytopenia, elevated liver transaminases, elevated lactate dehydrogenase, and elevated C-reactive protein and other inflammatory markers. Other abnormalities include neutrophilia, decreased haemoglobin, decreased albumin, and renal impairment.\[27\] \[28\] \[252\] \[138\] \[254\] \[272\] Laboratory abnormalities are less common in children.\[263\]

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.\[2\]
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.[2] In the UK, testing is now recommended in all people with symptoms of new continuous cough, high temperature, or altered sense of smell/taste.[273] Consult local health authorities for guidance as testing priorities will depend on local guidelines and available resources. See our Criteria section for CDC and Infectious Diseases Society of America recommendations on testing priorities.

Perform a nucleic acid amplification test, such as real-time reverse-transcription polymerase chain reaction (RT-PCR), for SARS-CoV-2 in appropriate patients with suspected infection, with confirmation by nucleic acid sequencing when necessary.[274]

- 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).

Interpreting the test result depends on the accuracy of the test, and the pretest probability (or estimated risk of disease) before testing. A positive result holds more weight than a negative test due to the test’s high specificity (around 95%) but moderate sensitivity (around 70%).[275]

False-negative rates of between 2% and 29% have been reported.[275] The probability of a false-negative result in an infected person decreases from 100% on day 1 of infection to 67% on day 4. The median false-negative rate drops to 38% on the day of symptom onset, decreases to 20% on day 8, and then starts to increase again from day 9.[276]

One or more negative results do not rule out the possibility of infection. If a negative result is obtained from a patient with a high index of suspicion for COVID-19 (or a high pretest probability), additional specimens should be collected and tested, especially if only upper respiratory tract specimens were collected initially.[274] 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.[277]

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.[2] [278]
Serological testing

Serological testing is becoming increasingly available for use; however, while rapid antibody detection kits have been approved in Europe and the US for the qualitative detection of SARS-CoV-2 immunoglobulin G (IgG)/IgM antibodies in serum, plasma, or whole blood, the World Health Organization does not recommend the use of these tests outside of research settings as they have not been validated as yet.[279]

The US Centers for Disease Control and Prevention recommends that serological assays that have received emergency-use authorisation from the Food and Drug Administration are preferred. There is no advantage of assays whether they test for IgG, IgM, IgM and IgG, or total antibody. The test’s positive predictive value should be high (99.5% or greater), and results should be interpreted in the context of the expected predictive values (positive and negative). Testing can be used to aid the diagnosis of patients who present 9 to 14 days after symptom onset. Serological tests should not be used to make decisions about people returning to their workplace.[280]

Antibody responses to SARS-CoV-2 typically occur during the first 1 to 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.[281] [282]

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

Chest imaging

All imaging procedures should be performed according to local infection prevention and control procedures to prevent transmission. Chest imaging is considered safe in pregnant women.[283]

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.[27] [28] [284]

Consider ordering a CT scan of the chest. CT imaging is the primary imaging modality in some countries, such as China. It may be helpful in making the diagnosis, guiding individual patient management decisions, aiding the diagnosis of complications, or giving clues to an alternative diagnosis. However, it is not diagnostic for COVID-19 and local guidance should be consulted on whether to perform a CT scan.

The British Society of Thoracic Imaging (BSTI) recommends CT imaging in patients with clinically suspected COVID-19 who are seriously ill if chest x-ray is uncertain or normal. Without the suspicion of COVID-19, the radiology is non-specific and could represent many other disease processes. The BSTI in collaboration with NHS England have produced a radiology decision support tool to help clinicians decide whether or not chest imaging should be ordered.[285]

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

Some institutions in the UK recommend a more pragmatic approach for patients with high clinical suspicion of COVID-19, with chest CT recommended only after two indeterminate or normal chest x-rays in combination with a negative RT-PCR test.[286]

The American College of Radiology recommends reserving CT for hospitalised, symptomatic patients with specific clinical indications for CT, and emphasises that a normal chest CT does not mean that a patient does not have COVID-19 and that an abnormal chest CT is not specific for COVID-19 diagnosis.[287]
Abnormal chest CT findings have been reported in up to 97% of COVID-19 patients in one meta-analysis of 50,466 hospitalised patients.[253] Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[288] CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients.[82][289] Some patients may present with a normal chest finding despite a positive RT-PCR.[290] Also, results of RT-PCR testing may be false-negative, so patients with typical CT findings should have repeat RT-PCR testing to confirm the diagnosis.[291]

Typical features

- Multiple bilateral lobular and subsegmental areas of ground-glass opacity or consolidation are seen in most patients, usually with a peripheral or posterior distribution, mainly in the lower lobes and less frequently in the right lower lobe. Consolidative opacities superimposed on ground-glass opacity may be found in a smaller number of cases, usually older patients.[27][292][293]
- Other classic findings include crazy-paving pattern, air bronchograms, and a reverse halo/perilobular pattern (i.e., organising pneumonia patterns).[285]
- 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.[294]
- Older people are more likely to have extensive lung lobe involvement, interstitial changes, and pleural thickening compared with younger patients.[295]
- Children may have signs of pneumonia on chest imaging despite having minimal or no symptoms.[269] Small nodular ground-glass opacities and consolidation with surrounding halo signs are typical in children.[269][296] Children tend to have more localised ground-glass opacity, lower ground-glass opacity attenuation, and relatively rare interlobular septal thickening.[297]

Atypical features

- Interlobular or septal thickening (smooth or irregular), thickening of the adjacent pleura, and subpleural involvement are atypical features. Some patients may rarely present with pleural effusion, pericardial effusion, bronchiectasis, cavitation, pneumothorax, lymphadenopathy, and round cystic changes. Atypical features appear to be more common in the later stages of disease, or on disease progression.[27][292][293]

Disease progression

- Abnormalities can rapidly evolve from focal unilateral to diffuse bilateral ground-glass opacities that progress to, or co-exist with, consolidations within 1 to 3 weeks.[289]
- 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.[293]

Sensitivity of CT

- In a cohort of over 1000 patients in a hyperendemic area in China, chest CT had a higher sensitivity for diagnosis of COVID-19 compared with initial RT-PCR from swab samples (88% versus 59%). Improvement of abnormal CT findings also preceded change from RT-PCR positivity to negativity in this cohort during recovery. The sensitivity of chest CT was 97% in patients who ultimately had positive RT-PCR results. However, in this setting, 75% of patients with negative RT-PCR results also had positive chest CT findings. Of these patients, 48% were considered highly likely cases, while 33% were considered probable cases.[298]
Emerging tests

Reverse transcription loop-mediated isothermal amplification

- Reverse transcription loop-mediated isothermal amplification (RT-LAMP) assays are an emerging test to detect SARS-CoV-2 viral RNA. While assays are simple and quick, there is less evidence for their use. Assays for SARS-CoV-2 have been developed and are being evaluated.[299] [300] [301]

Antigen testing

- In the US, the Food and Drug Administration has issued an emergency-use authorisation for the first COVID-19 antigen test. These tests detect fragments of proteins found on or within the virus by testing samples collected from nasal cavity swabs. The test works faster than RT-PCR; however, while it is very specific for the virus, it is not as sensitive, so a negative result should be followed up with a RT-PCR test.[302]

Lung ultrasound

- There is emerging evidence that lung ultrasound may be a useful aid in the diagnosis of COVID-19 as it has high sensitivity for detecting pleural thickening, subpleural consolidation, and ground-glass opacity. It has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, and repeatability during follow-up. However, it also has limitations (e.g., it is unable to discern chronicity of a lesion) and other imaging modalities may be required. Characteristic ultrasound patterns have been reported in patients with COVID-19 and include B-lines, white lung, pleural line thickening, and consolidations with air bronchograms.[303] [304] [305] [306]
- Ultrasound also appears to be a useful imaging modality in pregnant women and children.[307] [308]
- [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas]

Risk factors

Strong

residence in/travel to location reporting community transmission

- Diagnosis should be suspected in patients with acute respiratory illness (i.e., fever and at least one sign/symptom of respiratory disease such as cough or shortness of breath) and a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset.[132]

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.[132]

older age

- Older age is a risk factor for infection.[133] Data from a cross-sectional study in the UK indicate that people aged 40 to 64 years are at greatest risk of infection, followed by patients 75 years and older, and then people aged 65 to 74 years.[134] People aged 65 years and older are at higher risk for severe illness.[135] In the US, patients ≥65 years accounted for 31% of all cases, 45% of
hospitalisations, 53% of intensive care unit admissions, and 80% of deaths, with the highest incidence of severe outcomes in patients aged ≥85 years.[7]

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

- Widespread transmission has been reported in long-term care facilities.[55] People who live in a nursing home or long-term care facility are at higher risk for severe illness.[135] Care home residents represent approximately one third of the total number of deaths in England and Wales; other countries have reported a similar experience. This is likely due to shortages in personal protective equipment, a vulnerable population, and a lack of testing.[136] More than one third of care homes in England have had cases.[137]

**male sex**

- Male sex is a risk factor for infection.[133] Data from a cross-sectional study in the UK found that the adjusted odds of a positive test were greater in males (18.4%) compared with females (13.3%).[134] Male sex is also a risk factor for severe disease, disease progression, need for mechanical ventilation, and increased mortality.[4] [138] [139] It has been hypothesised that this may be due to the presence of androgens, or a lower level of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies compared with females; however, further research is required.[140] [141]

**ethnicity**

- Data from a cross-sectional study in the UK found that the adjusted odds of a positive test were greater in black people (62.1%) compared with white people (15.5%).[134] Early observational evidence from the UK also suggests that there is a higher mortality risk in Black, Asian, and minority ethnic (BAME) groups compared with white British groups, including healthcare workers. There is also evidence from the US that shows non-uniform deaths across BAME groups.[142] Data from a New York study found that 62% of critically ill patients admitted to two hospitals were Hispanic or Latin, 32% were White, 19% were Black, and 3% were Asian.[143] The reasons for this difference are not known.

**presence of comorbidities**

- People with comorbidities are at higher risk for severe illness and mortality.[135] [144] The most prevalent comorbidities in adults with COVID-19 are hypertension, cardiovascular disease, obesity, diabetes, smoking, respiratory disease, malignancy, and kidney disease.[145] [146] [147] In a prospective observational cohort study of more than 20,000 hospitalised patients in the UK, the most common comorbidities were chronic cardiac disease (31%), uncomplicated diabetes (21%), non-asthmatic chronic pulmonary disease (18%), and chronic kidney disease (16%).[6] It has been estimated that approximately 45% of adults in the US are at risk for complications from COVID-19 because of the presence of comorbidities. The risk is higher in people ages 80 years and older.[148] Approximately 39% of hospitalised children had an underlying condition in one study. The most prevalent comorbidities were asthma, neurological disorders, diabetes, obesity, cardiovascular disease, and malignancy/haematological conditions.[11]

**hypertension**

- Hypertension is associated with increased poor composite outcome, including mortality, severe COVID-19, acute respiratory distress syndrome, need for intensive care admission, and disease progression in patients with COVID-19.[149]
cardiovascular disease

- Underlying or previous history of cardiovascular disease is associated with severe disease and poor prognosis. Cardiovascular disease is associated with a 3-fold increased odds of severe infection, and an 11-fold increase in all-cause mortality.[150]

obesity

- Data from a cross-sectional study in the UK found that the adjusted odds of a positive test were greater in patients with obesity (20.9%) compared with those without (13.2%).[134] Data from France estimates that the prevalence of obesity is 1.35 times higher in patients with severe COVID-19 compared with the general population.[151] Obesity is a risk factor for severe disease, respiratory failure leading to invasive mechanical ventilation, and mortality.[152] Obesity may be a significant risk factor for the development of severe COVID-19 or mortality in younger people <60 years of age.[153] [154] [155] [156] Increased body mass index is a significant risk factor for severe disease in pregnant women.[157]

diabetes

- The pooled prevalence of diabetes in COVID-19 patients is approximately 10%. Prevalence is significantly higher in older patients and patients with severe COVID-19.[158] [159] [160] Diabetes is associated with increased risk of mortality, severe disease, disease progression, and acute respiratory distress syndrome.[161] Patients with diabetes have a 2-fold higher risk of developing severe disease, and a 2-fold higher risk of mortality.[159] Risk factors for poor prognosis and higher mortality include older age, elevated C-reactive protein, and insulin use.[162] One third of all deaths in hospitalised patients with COVID-19 in England occur in patients with diabetes. People with type 1 diabetes had 3.50 times the odds of dying in hospital with COVID-19, while people with type 2 diabetes had 2.03 times the odds.[163] Patients with type 2 diabetes who had well-controlled blood glucose had a lower risk of mortality compared with patients with poorly controlled blood glucose during hospitalisation.[164]

smoking

- Smoking is associated with disease progression and severe disease, with smokers having 1.91 times the odds of progression in COVID-19 severity compared with people who never smoked.[165] This may be due to increased airway expression of the angiotensin-converting enzyme-2 receptor in smokers.[166] However, data from a cross-sectional study in the UK found that the adjusted odds of a positive test were decreased in active smokers (11.4%) compared with non-smokers (17.9%).[134] The World Health Organization has reviewed the available evidence and concluded that smoking is associated with increased severity of disease and death in hospitalised patients.[167]

chronic respiratory disease

- There is no clear evidence that people with asthma or chronic obstructive pulmonary disease are at higher risk of infection.[168] However, patients with respiratory diseases such as cystic fibrosis, severe asthma, chronic obstructive pulmonary disease, interstitial lung disease, or pulmonary sarcoidosis may have an increased risk for severe disease, poor prognosis, and worse outcomes.[169] [170] [171] Chronic obstructive pulmonary disease is associated with a 5-fold increased risk of severe COVID-19 infection.[172] Asthma has been associated with a longer intubation time in those who require mechanical ventilation, especially in patients younger than 65 years.[173]
malignancy

- Patients with cancer are at a higher risk of infection, likely due to immunosuppressive treatments and/or recurrent hospital visits. They also had more severe outcomes (particularly those with metastatic disease, haematological cancer, or lung cancer) and appeared to deteriorate more quickly compared with patients without cancer. Patients who underwent cancer surgery had higher mortality rates. Children with cancer may be no more vulnerable to infection compared with children without cancer. Limited data show that the overall morbidity in paediatric patients with cancer is low, with only 5% requiring hospitalisation for symptoms.

chronic kidney disease

- Data from a cross-sectional study in the UK found that the adjusted odds of a positive test were greater in patients with chronic kidney disease (32.9%) compared with those without (14.4%).

chronic liver disease

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

metabolic dysfunction-associated fatty liver disease

- Patients with severe COVID-19 are more likely to have metabolic dysfunction-associated fatty liver disease (MAFLD; also called non-alcoholic fatty liver disease) compared with patients who have non-severe COVID-19. Severity of COVID-19 has been associated with younger age (<60 years) and intermediate or high fibrosis-4 (FIB-4) scores in patients with MAFLD.

organ transplant

- Organ transplant recipients may be at higher risk of severe illness or complications, more rapid clinical progression, and a prolonged clinical course compared with the general population due to chronic immunosuppression and the presence of co-existing conditions.

surgery

- Surgery may accelerate and exacerbate disease progression. A retrospective study of 34 patients in China who underwent elective surgeries during the incubation period of COVID-19 found that all patients developed pneumonia after surgery. Approximately 44% of these patients required admission to the intensive care unit, and 20% died.

air pollution

- Evidence suggests that there may be an association between long-term exposure to ambient air pollution and COVID-19. The highest numbers of cases were recorded in the most polluted regions of Italy, with patients presenting with more severe disease requiring intensive care. The mortality was 2-fold higher in polluted regions compared with other regions. One study found that of deaths from COVID-19 across 66 administrative regions in Italy, Spain, France, and Germany, 78% of deaths occurred in just five regions, and these regions were the most polluted in terms of nitrogen dioxide levels. A preprint study from Harvard University found that people who live in US regions with high levels of air pollution were more likely to die from COVID-19 than those who live in less polluted areas. The researchers found that an increase of 1 microgram/m³ in fine particulate matter is associated with an 8% increase in the COVID-19 death rate.
colder climate

- Emerging evidence suggests that weather conditions may influence the transmission of COVID-19, with cold and dry conditions appearing to increase transmission, and warm and humid conditions reducing the rate of infections. However, other data suggest that ambient temperature has no significant impact on transmission, especially during the pandemic stage of an emerging pathogen. Further research is required on how weather conditions influence transmission as colder temperatures have been associated with increased transmission of other coronaviruses. Higher latitude may also be associated with an increased risk of cases and deaths in some countries.

residence in urban or deprived areas

- Data from a cross-sectional study in the UK found that the adjusted odds of a positive test were greater in people living in urban areas (26.2%) compared with people living in rural areas (5.6%), and in people living in more deprived areas (29.5%) compared with people living in less deprived areas (7.7%).

ACE inhibitor/angiotensin-II receptor antagonist use

- There is concern that people on these drugs may be at increased risk of COVID-19 or more severe disease due to upregulation of angiotensin-converting enzyme-2 (ACE2) receptor expression. Some studies have shown that there is no association between the use of these drugs and testing positive for COVID-19. However, the UK National Institute for Health and Care Excellence states that conclusion cannot be drawn on whether these drugs increase or decrease the risk of developing COVID-19 or severe disease based on the current available evidence. Professional societies recommend that patients who are already on these drugs continue to take them.

immunosuppression

- Limited data suggest that immunosuppressed patients, including children and patients with inflammatory bowel disease, are not at increased risk of infection or severe illness; however, further research is required as there is concern about the risk of infection in these patients.

blood group A#

- There is some emerging anecdotal evidence that people with blood group A may be at higher risk of severe COVID-19 and hospitalisation, and blood group O may be associated with a protective effect. However, further research is required.

dysbiosis

- There is some emerging evidence that gut microbiota dysfunction may be implicated in the pathogenesis of COVID-19, although this is yet to be confirmed.

History & examination factors

Key diagnostic factors

fever (common)
• Reported in 77% to 98% of patients in case series.[27] [28] [252] [138] [253] [254] [309] In one case series, 44% of patients had a fever on presentation, but it developed in 89% of patients after hospitalisation.[75]
• Children may not present with fever, or may have a brief and rapidly resolving fever.[310] [311] [312]
• 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.[27] [28] [252] [138] [75] [253] [254] [309]
• Cough is usually dry.

dyspnoea (common)
• Reported in 18% to 57% of patients in case series.[27] [28] [252] [138] [75] [254] [309]
• Median time from onset of symptoms to development of dyspnoea is 5 to 8 days.[27] [28] [252]
• Less common in children compared with adults, but the most common sign in neonates.[263]

altered sense of smell/taste (common)
• The pooled prevalence of olfactory dysfunction (anosmia/hyposmia) was 53% in one meta-analysis, with a pooled prevalence of 44% for gustatory dysfunction (ageusia/dysgeusia).[313] Prevalence appears to be higher in European studies; 87% of patients self-reported loss of smell and 56% reported taste dysfunction in one study.[314]
• Initial findings from the American Academy of Otolaryngology - Head and Neck Surgery’s COVID-19 anosmia reporting tool found that 73% of patients reported anosmia prior to diagnosis, and it was the initial symptom in 26.6% of patients.[315]
• There is anecdotal evidence that altered sense of smell/taste may be an early symptom of COVID-19, or may be the only symptom in patients with mild to moderate illness.[316]
• The UK government now includes altered sense of taste/smell in the general clinical case definition, and recommends that patients self-isolate if they develop an altered sense of smell/taste. However, the current evidence base is of poor quality due to the mainly retrospective and cross-sectional nature of studies available.[317] [318]

Other diagnostic factors

fatigue (common)
• Reported in 29% to 69% of patients in case series.[27] [252] [75] [254] [309]
• Patients may also report malaise.

myalgia (common)
• Reported in 11% to 44% of patients in case series.[27] [28] [252] [75] [253] [309]
• Arthralgia has also been reported.
• Myositis secondary to COVID-19 infection and presenting with myalgia has been reported in one case.[319]

sputum production/expectoration (common)
• Reported in 26% to 33% of patients in case series.[27] [252] [75] [309]

sore throat (common)
• Reported in 5% to 17% of patients in case series, and usually presents early in the clinical course.[28] [252] [75] [309]

gastrointestinal symptoms (uncommon)

• Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea, abdominal pain, loss of appetite) have been reported commonly. The pooled prevalence of gastrointestinal symptoms was 15% in a meta-analysis, and patients with severe illness had a higher rate of gastrointestinal symptoms. Around 10% of patients presented with gastrointestinal symptoms alone.[320] Pooled prevalence estimates for specific gastrointestinal symptoms were 7.8% for nausea/vomiting, 7.7% for diarrhoea, and 2.7% for abdominal pain; however, most studies reported on hospitalised patients. Gastrointestinal symptoms were more prevalent outside of China.[321]

• Gastrointestinal symptoms are not associated with an increased likelihood for testing positive for COVID-19; however, anorexia and diarrhoea, when combined with loss of smell/taste and fever, were 99% specific for COVID-19 infection in one prospective case-control study.[322]

• Haematochezia has been reported.[323]

confusion/delirium (uncommon)

• Confusion has been reported in 9% of patients in case series.[28]

• Patients may rarely present with delirium, which may be severe. Rapid onset of delirium may indicate clinical deterioration. It may be caused by hypoxia, central nervous system infection, adverse effects from drugs, or multi-organ failure. Causes are often multifactorial.[324] [325] [326] [327]

dizziness (uncommon)

• Reported in 9% to 12% of patients in case series.[252] [254]

headache (uncommon)

• Reported in 6% to 14% of patients in case series.[27] [28] [252] [75] [254] [309]

rhinorrhoea or nasal congestion (uncommon)

• Reported in 4% to 5% of patients in case series.[28] [75]

• Nasal congestion has been reported in nearly 4% of patients in one case series.[328]

haemoptysis (uncommon)

• Reported in 1% to 5% of patients in case series.[27] [75]

• May be a symptom of pulmonary embolism.[329]

chest pain (uncommon)

• Reported in 2% to 5% of patients in case series.[27] [28]

• May indicate pneumonia.

conjunctivitis (uncommon)

• Ocular manifestations consistent with conjunctivitis (i.e., conjunctival hyperaemia, chemosis, epiphora, and increased secretions) were reported in 32% of patients in one case series.[330] However, a meta-analysis of over 1100 patients found the overall rate of conjunctivitis to be significantly lower at 1.1%. [331] Conjunctivitis appears to be more frequent in patients with severe illness.[330] It may be the only presenting symptom in some patients.[332]

cutaneous manifestations (uncommon)
• Reported in 7.8% of hospitalised adults in one observational cross-sectional study in Italy.[333]
• Various manifestations have been reported in adults and children including a erythematous or maculopapular or morbilliform rash, a varicella-like papulovesicular exanthem on the trunk, petechiae, urticaria, vesicles, ischaemic and ecchymotic acral lesions as a manifestation of clotting disorders, pityriasis rosea, digitate papulosquamous eruption, and erythema multiforme-like lesions.[334] [335] [336] [337] [338] [339] [340] [341] [342]
• Chilblains, particularly on the toes or foot, are an emerging symptom, especially in younger patients (including children) who lack a history of chilblains, Raynaud's phenomenon, or collagen vascular diseases (e.g., systemic lupus erythematosus).[343] [344] [345]
• A case collection survey of images and clinical data classified lesions as: maculopapular eruptions (47%); acral areas of erythema with vesicles or pustules, or pseudo-chilblain (19%); urticarial lesions (19%); other vesicular eruptions (9%); and livedo or necrosis (6%). Vesicular lesions often appear early in the course of disease before other symptoms, and the pseudo-chilblain pattern frequently appears later in the course after the appearance of other symptoms.[346]
• It is unclear whether skin lesions are from viral infection, systemic consequences of the infection, or drugs the patient may be on. Further data is required to better understand skin involvement.

bronchial breath sounds (uncommon)
• May indicate pneumonia.

tachypnoea (uncommon)
• May be present in patients with acute respiratory distress.

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

cyanois (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

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>pulse oximetry</td>
<td>may show low oxygen saturation (SpO₂ &lt;90%)</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Recommended in patients with respiratory distress and cyanosis.</td>
<td></td>
</tr>
<tr>
<td>• Clinicians should be aware that patients with COVID-19 can develop ‘silent hypoxia’: their oxygen saturations can drop to low levels and precipitate acute respiratory failure without the presence of obvious symptoms of respiratory distress. Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognising further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[270]</td>
<td></td>
</tr>
<tr>
<td>ABG</td>
<td>may show low partial oxygen pressure</td>
</tr>
<tr>
<td>• Order in patients with severe illness as indicated to detect hypercarbia or acidosis.</td>
<td></td>
</tr>
<tr>
<td>• Recommended in patients with respiratory distress and cyanosis who have low oxygen saturation (SpO₂ &lt;90%).</td>
<td></td>
</tr>
<tr>
<td>FBC</td>
<td>lymphopenia; leukocytosis; thrombocytopenia; decreased haemoglobin; decreased eosinophils#</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Lymphopenia, leukocytosis, and thrombocytopenia are associated with severe disease; therefore, they may be useful as biomarkers for predicting disease progression.[347]</td>
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<tr>
<td>• High neutrophil-to-lymphocyte ratio is a useful marker for indicating risk for severe illness and poor prognosis.[348] [349]</td>
<td></td>
</tr>
<tr>
<td>comprehensive metabolic panel</td>
<td>elevated liver transaminases; decreased albumin; renal impairment</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• The most common laboratory abnormalities in patients hospitalised with pneumonia include elevated liver transaminases. Other abnormalities include decreased albumin and renal impairment.[27] [28]</td>
<td></td>
</tr>
<tr>
<td>• Serum urea and creatinine levels increase in severe disease; therefore, they may be useful as biomarkers for predicting disease progression.[347]</td>
<td></td>
</tr>
<tr>
<td>• Liver function abnormalities may be more common in patients with COVID-19 compared with other types of pneumonia.[294]</td>
<td></td>
</tr>
<tr>
<td>blood glucose level</td>
<td>variable</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Uncontrolled hyperglycaemia has been shown to worsen prognosis in all patients, not only patients with diabetes.[350] [351] [352]</td>
<td></td>
</tr>
<tr>
<td>coagulation screen</td>
<td>elevated D-dimer; prolonged prothrombin time; elevated fibrinogen</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• The most common abnormalities are elevated D-dimer and fibrinogen, and prolonged prothrombin time.[27] [28] [252] [353]</td>
<td></td>
</tr>
<tr>
<td>• D-dimer levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[347]</td>
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<tr>
<td>Test</td>
<td>Result</td>
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<tr>
<td>• Patients with very high D-dimer levels have an increased risk of thrombosis.[354] [355]</td>
<td></td>
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<tr>
<td>serum C-reactive protein</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[347] [356]</td>
<td></td>
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<tr>
<td>serum lactate dehydrogenase</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[347]</td>
<td></td>
</tr>
<tr>
<td>• May be more common in patients with COVID-19 compared with other types of pneumonia.[294]</td>
<td></td>
</tr>
<tr>
<td>serum interleukin-6 level</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Interleukin-6 is the most common cytokine released by activated macrophages. Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[347] [357] It is less likely to be elevated in children.[358]</td>
<td></td>
</tr>
<tr>
<td>cardiac biomarkers</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
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</tr>
<tr>
<td>• Serum troponin I level may be elevated in patients with cardiac injury. Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[347]</td>
<td></td>
</tr>
<tr>
<td>• Other cardiac biomarkers (e.g., creatine kinase-myocardial band, brain natriuretic peptide, cardiac troponin T) may also be elevated and are associated with severe disease and worse outcomes.[359] [360]</td>
<td></td>
</tr>
<tr>
<td>serum procalcitonin</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[361]</td>
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<tr>
<td>• May be elevated in patients with secondary bacterial infection.[27] [28] May be more common in children.[269]</td>
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<tr>
<td>• There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about the use of antibiotics.[362]</td>
<td></td>
</tr>
<tr>
<td>• However, it may be helpful in limiting overuse of antibiotics in patients with COVID-19-related pneumonia.[363]</td>
<td></td>
</tr>
<tr>
<td>serum ferritin level</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• May indicate development of cytokine release syndrome.[364]</td>
<td></td>
</tr>
<tr>
<td>serum amyloid A level</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[347]</td>
<td></td>
</tr>
<tr>
<td>serum creatine kinase</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated creatine kinase has been reported in 13% to 33% of patients.[27] [28]</td>
<td></td>
</tr>
<tr>
<td>• Indicates muscle or myocardium injury.</td>
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<tr>
<td>Test</td>
<td>Result</td>
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<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>blood and sputum cultures</strong></td>
<td>negative for bacterial infection</td>
</tr>
<tr>
<td>• Collect blood and sputum specimens for culture in all patients to</td>
<td></td>
</tr>
<tr>
<td>rule out other causes of lower respiratory tract infection and sepsis,</td>
<td></td>
</tr>
<tr>
<td>especially patients with an atypical epidemiological history.[2]</td>
<td></td>
</tr>
<tr>
<td>• Testing is most useful when there is concern for multidrug-resistant</td>
<td></td>
</tr>
<tr>
<td>pathogens.[363]</td>
<td></td>
</tr>
<tr>
<td>• Specimens should be collected prior to starting empirical antimicrobials if possible.</td>
<td></td>
</tr>
<tr>
<td><strong>real-time reverse transcription polymerase chain reaction (RT-PCR)</strong></td>
<td>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</td>
</tr>
<tr>
<td>• Molecular testing is required to confirm the diagnosis. Nucleic acid</td>
<td></td>
</tr>
<tr>
<td>sequencing may be required to confirm the diagnosis.[274] Priorities</td>
<td></td>
</tr>
<tr>
<td>for testing depend on local guidelines and available resources.</td>
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</tr>
<tr>
<td>• The positive predictive value ranged from 47.3% to 96.4%, and the</td>
<td></td>
</tr>
<tr>
<td>negative predictive value ranged from 96.8% to 99.9% in one meta-</td>
<td></td>
</tr>
<tr>
<td>analysis. Pooled sensitivity was 89%.[365]</td>
<td></td>
</tr>
<tr>
<td>• 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.[274]</td>
<td></td>
</tr>
<tr>
<td>• There are little data available on the rates of false-positive and false-negative results for the various RT-PCR tests available; however, both have been reported. If a negative result is obtained from a patient with a high index of suspicion for COVID-19, additional specimens should be collected and tested, especially if only upper respiratory tract specimens were collected initially.[274]</td>
<td></td>
</tr>
<tr>
<td>• Many tests are available under the US Food and Drug Administration’s emergency-use authorisation scheme.</td>
<td></td>
</tr>
<tr>
<td>• A point-of-care test that provides results within hours is available in some countries.[366] While rapid point-of-care tests are available, the World Health Organization does not recommend the use of these tests outside of research settings as they have not been validated as yet.[279] A pooled sensitivity of 64.8% and specificity of 98% has been reported with point-of-care tests.[367]</td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>• Sensitivity and specificity of RT-PCR for diagnostic testing are unknown.[368]</td>
<td></td>
</tr>
<tr>
<td>• Collect nasopharyngeal swabs to rule out influenza and other respiratory infections according to local guidance. It is important to note that co-infections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19.[2] [278]</td>
<td></td>
</tr>
<tr>
<td>• There is emerging evidence that saliva may be a reliable specimen for detecting SARS-CoV-2 by RT-PCR.[369] [370] A test that uses saliva has just been approved.[371]</td>
<td></td>
</tr>
<tr>
<td>• The Food and Drug Administration has approved the first diagnostic test in the US with a home collection option, which allows for testing of a sample taken from the nose using a self-collection kit. After the</td>
<td></td>
</tr>
</tbody>
</table>
## Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>sample is taken, it is sent in an insulated package to a designated laboratory for testing.</td>
<td></td>
</tr>
<tr>
<td><strong>chest x-ray</strong></td>
<td><strong>unilateral or bilateral lung infiltrates</strong></td>
</tr>
<tr>
<td>• Order in all patients with suspected pneumonia.</td>
<td></td>
</tr>
<tr>
<td>• Unilateral lung infiltrates are found in 25% of patients, and bilateral lung infiltrates are found in 75% of patients.</td>
<td></td>
</tr>
</tbody>
</table>
### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
</table>
| computed tomography (CT) chest | - Consider a CT scan of the chest. Consult local guidance on whether to perform a CT scan.  
- The positive predictive value was low (1.5% to 30.7%) in low-prevalence regions, and the negative predictive value ranged from 95.4% to 99.8% in one meta-analysis. Pooled sensitivity and specificity were 94% and 37%, respectively.[365]  
- The British Society of Thoracic Imaging (BSTI) recommends CT imaging in patients with clinically suspected COVID-19 who are seriously ill if chest x-ray is uncertain or normal. [BSTI: radiology decision tool for suspected COVID-19] Some institutions in the UK recommend a more pragmatic approach for patients with high clinical suspicion of COVID-19, with chest CT recommended only after two indeterminate or normal chest x-rays in combination with a negative RT-PCR test.[286] The American College of Radiology recommends reserving CT for hospitalised, symptomatic patients with specific clinical indications for CT, and emphasises that a normal chest CT does not mean that a patient does not have COVID-19 and that an abnormal chest CT is not specific for COVID-19 diagnosis.[287]  
- Abnormal chest CT findings have been reported in up to 97% of hospitalised patients.[253] Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[288] CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients.[82][289] Some patients may present with a normal chest finding despite a positive RT-PCR.[290] Also, results of RT-PCR testing may be false-negative, so patients with typical CT findings should have repeat RT-PCR testing to confirm the diagnosis.[291]  
- Atypical features appear to be more common in the later stages of disease, or on disease progression.[27][292][293]  
- Older people are more likely to have extensive lung lobe involvement, interstitial changes, and pleural thickening compared with younger patients.[295]  
- Small nodular ground-glass opacities and consolidation with surrounding halo signs are typical in children.[269][296] Children tend to have more localised ground-glass opacity, lower ground-glass opacity attenuation, and relatively rare interlobular septal thickening.[297]  
- 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.[289] 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.[293]  
- 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 typical features: multiple bilateral lobular and subsegmental areas of ground-glass opacity or consolidation (usually peripheral or posterior, mainly in the lower lobes, less frequently in right lower lobe), crazy-paving pattern, air bronchograms, reverse halo/perilobular pattern; atypical features: interlobular or septal thickening (smooth or irregular), thickening of the adjacent pleura, subpleural involvement, pleural effusion, pericardial effusion, bronchiectasis, cavitation, pneumothorax, lymphadenopathy, round cystic changes |
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>these patients, 48% were considered highly likely cases, while 33% were considered probable cases.[298] [Fig-2]</td>
<td>positive for SARS-CoV-2 virus antibodies</td>
</tr>
</tbody>
</table>

**serology**

- Serological testing is becoming increasingly available for use; however, while rapid antibody detection kits have been approved in Europe and the US for the qualitative detection of SARS-CoV-2 IgG/ IgM antibodies in serum, plasma, or whole blood, the World Health Organization does not recommend the use of these tests outside of research settings as they have not been validated as yet.[279]
- The US Centers for Disease Control and Prevention recommends that serological assays that have received emergency-use authorisation from the Food and Drug Administration are preferred. There is no advantage of assays whether they test for IgG, IgM, IgM and IgG, or total antibody. The test’s positive predictive value should be high (99.5% or greater), and results should be interpreted in the context of the expected predictive values (positive and negative). Testing can be used to aid the diagnosis of patients who present 9 to 14 days after symptom onset. Serological tests should not be used to make decisions about people returning to their workplace.[280]
- Antibody responses to SARS-CoV-2 typically occur during the first 1 to 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.[281] [282] Serum samples can be stored to retrospectively define cases when validated serology tests become available.
## Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>antigen test</strong></td>
<td>positive for SARS-CoV-2 virus antigen</td>
</tr>
<tr>
<td>• In the US, the Food and Drug Administration has issued an emergency-use authorisation for the first COVID-19 antigen test. These tests detect fragments of proteins found on or within the virus by testing samples collected from nasal cavity swabs. The test works faster than RT-PCR; however, while it is very specific for the virus, it is not as sensitive, so a negative result should be followed up with a RT-PCR test.[302]</td>
<td></td>
</tr>
<tr>
<td><strong>reverse transcription loop-mediated isothermal amplification (RT-LAMP)</strong></td>
<td>positive for SARS-CoV-2 viral RNA</td>
</tr>
<tr>
<td>• A similar process to RT-PCR, but uses constant temperatures and produces more viral DNA compared with RT-PCR. While simple and quick, it is a newer technology and there is less evidence for its use. Assays for SARS-CoV-2 have been developed and are being evaluated.[299] [300] [301]</td>
<td></td>
</tr>
<tr>
<td><strong>lung ultrasound</strong></td>
<td>B-lines; white lung; pleural line thickening; consolidations with air bronchograms</td>
</tr>
<tr>
<td>• There is emerging evidence that lung ultrasound may be a useful aid in the diagnosis of COVID-19 as it has high sensitivity for detecting pleural thickening, subpleural consolidation, and ground-glass opacity. It has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, and repeatability during follow-up. However, it also has limitations (e.g., it is unable to discern chronicity of a lesion) and other imaging modalities may be required.[303] [304] [305] [306] Ultrasound also appears to be a useful imaging modality in pregnant women and children.[307] [308]</td>
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<td>• [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas]</td>
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### Differential diagnosis

<table>
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<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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| **Community-acquired pneumonia** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
• Differentiating COVID-19 from community-acquired bacterial pneumonia is not usually possible from signs and symptoms. However, patients with bacterial pneumonia are more likely to have rapid development of symptoms and purulent sputum. They are less likely to have myalgia, anosmia, or pleuritic pain. [373] [374] | • Blood or sputum culture or molecular testing: positive for causative organism.  
• RT-PCR: negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA (co-infections are possible).  
• CT chest: centrilobular nodules, mucoid impactions. [375] |
| **Influenza infection**    | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.  
• A small case-control study found that new-onset smell and/or taste disorders were more common among patients with COVID-19 compared with patients with influenza. [376] | • RT-PCR: positive for influenza A or B viral RNA; negative for SARS-CoV-2 viral RNA (co-infections are possible).  
• CT chest: there is emerging evidence that CT can be used for differentiating between influenza and COVID-19. COVID-19 patients are more likely to have rounded opacities and interlobular septal thickening, but less likely to have nodules, tree-in-bud sign, and pleural effusion. [377]  
• Inflammatory markers and coagulation screen: there is emerging evidence that inflammatory markers (lactate dehydrogenase, erythrocyte sedimentation rate, C-reactive protein) and coagulation parameters are not as high in patients with influenza compared with COVID-19. [378] |
| **Common cold**            | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.  
• A small case-control study found that new-onset smell and/or taste disorders were more common among patients with COVID-19 compared with patients with influenza. [376] | • RT-PCR: positive for causative organism; negative for SARS-CoV-2 viral RNA (co-infections are possible). |
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<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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<tr>
<td>Suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.</td>
<td>• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.</td>
<td>• Blood or sputum culture of molecular testing: positive for causative organism. • RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible).</td>
</tr>
<tr>
<td>Other viral or bacterial respiratory infections</td>
<td>• Lack of residence in travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset. • Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. • Adenovirus and <em>Mycoplasma</em> should be considered in clusters of pneumonia patients, especially in closed settings such as military camps and schools.</td>
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<td>Aspiration pneumonia</td>
<td>• Lack of residence in travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset. • Differentiating COVID-19 from aspiration pneumonia is not usually possible from signs and symptoms.</td>
<td>• RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible). • CT chest: difficult to distinguish on CT; however, anterior lung involvement may be more suggestive of COVID-19 pneumonia.[379]</td>
</tr>
<tr>
<td>Pneumocystis jirovecii pneumonia</td>
<td>• Lack of residence in travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset. • Differentiating COVID-19 from pneumocystis jirovecii pneumonia is not usually possible from signs and symptoms. • Patients are usually immunocompromised (e.g.,</td>
<td>• Sputum culture: positive for <em>Pneumocystis</em> . • RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible). • CT chest: ground-glass opacity is usually more diffusely distributed with a tendency to spare the subpleural regions.[375]</td>
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<tr>
<td>Condition</td>
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<td>HIV positive) and duration of symptoms may be longer.</td>
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</table>
| **Middle East respiratory syndrome (MERS)** | • Travel history to the Middle East or contact with a confirmed case of MERS.  
• Differentiating COVID-19 from MERS is not possible from signs and symptoms.  
• Initial data suggest that the clinical course of COVID-19 is less severe and the case fatality rate is lower compared with MERS. | • Reverse-transcriptase polymerase chain reaction (RT-PCR): positive for MERS-CoV viral RNA. |
| **Severe acute respiratory syndrome (SARS)** | • There have been no cases of SARS reported since 2004. | • RT-PCR: positive for severe acute respiratory syndrome coronavirus (SARS-CoV) viral RNA. |
| **Avian influenza A (H7N9) virus infection** | • May be difficult to differentiate based on 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 where avian influenza is endemic. | • RT-PCR: positive for H7-specific viral RNA. |
| **Avian influenza A (H5N1) virus infection** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
• Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area where avian influenza is endemic. | • RT-PCR: positive for H5N1 viral RNA. |
| **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. |
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|                       | • 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.[380]  
  • Symptoms of COVID-19 and neutropenic sepsis may be difficult to differentiate at initial presentation.                                      | • CBC: neutropenia.  
  • RT-PCR: negative for SARS-CoV-2 viral RNA.                                                     |

**Diagnostic criteria**

**World Health Organization: case definitions[132]**

**Suspect case**

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

**Probable case**

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

**Confirmed case**

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

**Definition of contact**

- A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:
• Face-to-face contact with a probable or confirmed case within 1 metre (3 feet) and for more than 15 minutes
• Direct physical contact with a probable or confirmed case
• Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment
• Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken that led to confirmation.

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

Centers for Disease Control and Prevention: criteria to guide evaluation and laboratory testing for COVID-19[381]

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[382]

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

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.

Severe COVID-19: location of care and admission

Promptly admit patients with pneumonia or acute respiratory distress to an appropriate healthcare facility and start supportive care depending on the clinical presentation. The strongest risk factors for hospital admission are older age (odds ratio of >2 for all age groups older than 44 years, and odds ratio of 37.9 for people ages 75 years and over), heart failure, male sex, chronic kidney disease, and increased body mass index (BMI).[387] Approximately 14% of patients in China presented with severe illness requiring oxygen therapy.[4] Children are less likely to require hospitalisation, but if admitted, generally only require supportive care.[10] [17]

Admit patients with impending or established respiratory failure to an intensive care unit. Approximately 5% of patients in China presented with critical illness requiring intensive care unit treatment.[4] The most common reasons for intensive care unit admission are hypoxaemic respiratory failure leading to mechanical ventilation and hypotension.[388] Data from a New York study found that 22% of patients had hypoxaemic respiratory failure, and approximately 79% of patients required invasive mechanical ventilation.[143] The strongest risk factors for critical illness are oxygen saturation <88%; elevated serum troponin, C-reactive protein, and D-dimer; and, to a lesser extent, older age, BMI >40, heart failure, and male sex.[387]

The median time from onset of symptoms to hospital admission is reported to be approximately 7 days.[27] [389]

Treatment and care planning

- Discuss the risks, benefits, and potential outcomes of treatment options with patients and their families, and allow them to express preferences about their management. Take their wishes and expectations into account when considering the ceiling of treatment. Use decision support tools if available. Put treatment escalation plans in place, and discuss any existing advance care plans or advance decisions to refuse treatment with patients who have pre-existing advanced comorbidities.[390]

Admission to critical care

- Assess all adults for frailty on admission to hospital, irrespective of age and COVID-19 status, using the Clinical Frailty Scale (CFS). [Clinical frailty scale]
- Involve critical care teams in discussions about admission to critical care for patients where:
  - The CFS score suggests the person is less frail (e.g., CFS <5), they are likely to benefit from critical care organ support, and the patient wants critical care treatment; or
  - The CFS score suggests the person is more frail (e.g., CFS ≥5), there is uncertainty regarding the benefit of critical care organ support, and critical care advice is needed to help the decision about treatment.
• Take into account the impact of underlying pathologies, comorbidities, and severity of acute illness.[391]

Severe COVID-19: supportive care

Oxygen

• Give supplemental oxygen at a rate of 5 L/minute to patients with severe acute respiratory infection and respiratory distress, hypoxaemia, shock, or SpO₂ <90%.[2] [392] Titrate flow rates to reach a target SpO₂ ≥94% during resuscitation.[2] 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 SpO₂ 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.[2] Some guidelines recommend that SpO₂ should be maintained no higher than 96%.[392]
• Some locations may recommend different targets in order to support prioritisation of oxygen flow for the most severely ill patients in hospital. For example, NHS England recommends a target of 92% to 95% (or 90% to 94% if clinically appropriate).[393]
• Oxygen delivery in patients with severe hypoxaemia can be increased by using a non-rebreathing mask and prone positioning.[394]
• Early self-proning of awake, non-intubated patients improved oxygen saturation in a small pilot study of 50 patients in a New York emergency department.[395]
• There is no evidence of benefit for oxygen therapy in patients with COVID-19 in the absence of hypoxaemia.[396]

Intravenous fluids

• Manage fluids conservatively in adults and children with severe acute respiratory infection when there is no evidence of shock as aggressive fluid resuscitation may worsen oxygenation.[2]

Acid-base or electrolyte abnormalities

• Correct any abnormalities, such as hyperglycaemia or metabolic acidosis, according to local protocols.[397]

Antimicrobials

• Consider starting empirical antimicrobials if there is clinical suspicion of bacterial infection. Do not wait for microbiology results. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria, or within 4 hours of establishing a diagnosis of pneumonia. Choice of empirical antimicrobials should be based on the clinical diagnosis, availability, and local epidemiology, resistance, and susceptibility data.[2] [362]
• Some guidelines recommend empirical antimicrobials for bacterial pathogens in all patients with community-acquired pneumonia without confirmed COVID-19. It is likely that the bacterial pathogens in patients with COVID-19 and pneumonia are the same as in previous patients with community-acquired pneumonia, and therefore empirical antimicrobial recommendations should be the same.[363]
• However, the National Institute for Health and Care Excellence (NICE) in the UK recommends that it is reasonable not to start empirical antimicrobials if you are confident that the clinical features are typical for COVID-19.[362] There is insufficient evidence to recommend empirical broad-spectrum antimicrobials in the absence of another indication.[3]
• Consider treatment with a neuraminidase inhibitor until influenza is ruled out.[2]
• Reassess antimicrobial use daily in order to minimise the consequences of unnecessary antimicrobial therapy. De-escalate empirical therapy based on microbiology results and clinical judgement.[2]
• Some patients may require continued antimicrobial therapy once COVID-19 has been confirmed depending on the clinical circumstances (e.g., clinical or microbiological evidence of bacterial infection regardless of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] test results, SARS-CoV-2 test result is positive but clinical features are not typical for COVID-19). In these circumstances, review antibiotic choice based on microbiology results and switch to a narrower-spectrum antibiotic if appropriate, review intravenous antibiotic use within 48 hours and consider switching to oral therapy, and give for a total of 5 days unless there is a clear indication to continue.[362]

Venous thromboembolism (VTE) prophylaxis

• Start appropriate VTE prophylaxis in hospitalised adults with COVID-19 as per the standard of care for other hospitalised adults without COVID-19, provided there are no contraindications. A COVID-19 diagnosis should not influence a paediatrician's recommendations about VTE prophylaxis in hospitalised children. Pregnant women should be managed by a specialist.[3] [398]
• Low molecular weight heparin or fondaparinux are preferred over unfractionated heparin in order to reduce patient contact. Unfractionated heparin is contraindicated in patients with severe thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia. Mechanical thromboprophylaxis is recommended if anticoagulation is contraindicated or not available.[399]
• The optimal anticoagulant dose for VTE prophylaxis in COVID-19 patients is unknown. Some clinicians are using intermediate- or full-dose regimens rather than prophylactic doses as they are worried about undetected thrombi; however, this may lead to major bleeding events.[400] There are insufficient data to recommend increased anticoagulant doses for VTE prophylaxis in COVID-19 patients outside the setting of a clinical trial.[3] However, some guidelines recommend that escalated doses can be considered in critically ill patients.[398]
• Routine post-discharge VTE prophylaxis is not recommended, except in certain high-risk patients.[3] [398]
• There is little high-quality guidance for VTE prophylaxis in COVID-19 patients; therefore, clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[398]

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.[2]

Prevention of complications

• Implement standard interventions to prevent complications associated with critical illness.[2] Complications such as acute respiratory distress syndrome (ARDS), sepsis, and septic shock should be managed according to usual protocols. See our Complications section for more information.
Palliative care

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

**Severe COVID-19: symptom management**

### Managing fever

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

- Some clinicians have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen could worsen COVID-19 or have a negative impact on disease outcome based on anecdotal reports and the fact these drugs can mask symptoms of bacterial infections. There is currently no strong evidence to support this. The European Medicines Agency, the US Food and Drug Administration, and the Commission of Human Medicines do not recommend avoiding NSAIDs in COVID-19 when clinically indicated. The WHO has confirmed that there is no evidence at present of severe adverse events in COVID-19 patients taking NSAIDs, or effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19. NICE has updated its guidance to recommend either paracetamol or ibuprofen for the treatment of fever; however, it recommends taking the lowest effective dose of ibuprofen for the shortest period needed to control symptoms.

### Managing cough

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

### Managing olfactory dysfunction

- Consider treatment if this symptom persists beyond 2 weeks. Olfactory dysfunction often improves spontaneously and does not require specific treatment. Treatments used in post-infectious olfactory dysfunction (e.g., olfactory training) may be potentially helpful, but there is no evidence to support the use of these treatments in patients with COVID-19.

### Managing breathlessness

- Keep the room cool, and encourage relaxation, breathing techniques, and changing body positions. Identify and treat any reversible causes of breathlessness (e.g., pulmonary oedema). Consider a trial of oxygen, if available. Consider an opioid and benzodiazepine combination in patients with moderate to severe breathlessness or patients who are distressed.

### Managing anxiety, delirium, and agitation

- Identify and treat any reversible causes (e.g., offer reassurance, treat hypoxia). Consider a benzodiazepine for the management of anxiety or agitation. Consider haloperidol or a phenothiazine for the management of delirium. Non-pharmacological interventions are the mainstay for the management of delirium when possible, and prevention is key.
Severe COVID-19: high flow nasal oxygen/non-invasive ventilation

Provide advanced oxygen or non-invasive ventilation in patients who are deteriorating and failing to respond to standard oxygen therapy.[2] Indirect and low-certainty evidence suggests that non-invasive ventilation probably reduces mortality in patients with COVID-19, similar to mechanical ventilation, but may increase the risk of transmission.[412]

Follow local infection prevention and control procedures to prevent transmission to healthcare workers, especially when performing aerosol-generating procedures. Novel methods to protect clinicians without access to standard personal protective equipment during aerosol-generating procedures have been suggested (e.g., aerosol box, plastic drapes, helmet devices, plastic negative pressure canopy).[413] [414] [415] [416]

Consider a trial of high-flow nasal oxygen or non-invasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in patients with hypoxaemic respiratory failure.[2] [392] These procedures may avoid the need for intubation and mechanical ventilation; however, they have a higher risk of aerosol generation.[417]

There is ongoing debate about the optimal mode of respiratory support before mechanical ventilation, and you should check local guidelines for preferred options.[418] NHS England recommends CPAP as the preferred form of non-invasive ventilation, and doesn't advocate the use of high-flow nasal oxygen based on a lack of efficacy, oxygen use, and infection spread. High-flow oxygen delivery can place a strain on oxygen supplies with the risk of site supply failure. Early CPAP may provide a bridge to invasive mechanical ventilation. Use of BiPAP should be reserved for patients with hypercapnic acute or chronic ventilatory failure.[419] The US National Institutes of Health (NIH) recommends high-flow nasal oxygen for acute hypoxaemic respiratory failure over non-invasive positive pressure ventilation, unless high-flow nasal oxygen is not available.[3] Despite the trend to avoid high-flow nasal oxygen, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[420]

Monitor patients closely for clinical deterioration that could result in the need for urgent intubation.[2] Patients with lower PaO₂/fraction of inspired oxygen (FiO₂) were more likely to experience failure with high-flow nasal oxygen and require ventilation in one study.[421]

Severe COVID-19: mechanical ventilation

Consider intubation and mechanical ventilation in patients who are acutely deteriorating despite advanced oxygen/non-invasive ventilatory support measures, especially those with fatigue and at risk for exhaustion because of respiratory distress. Two-thirds of patients who required critical care in the UK had mechanical ventilation within 24 hours of admission.[422] In New York, 33% of hospitalised patients developed respiratory failure leading to mechanical ventilation. These patients were more likely to be male, have obesity, and have elevated inflammatory markers and liver function tests.[138] Patients in a New York study spent an average of 18 days on a ventilator (range 9-28 days). This corresponds to reports from Italy.[143]

Endotracheal intubation should be performed by an experienced provider using airborne precautions. Intubation by video laryngoscopy is recommended if possible.[3] Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require pre-oxygenation with 100% FiO₂ for 5 minutes.[2]

The WHO, National Institutes of Health, and Surviving Sepsis Campaign guidelines recommend that mechanically ventilated patients with ARDS should receive a lung-protective, low tidal volume/low
inspiratory pressure ventilation strategy (lower targets are recommended in children). A higher positive end-expiratory pressure (PEEP) strategy is preferred over a lower PEEP strategy.[2] [392] [3]

Although some patients with COVID-19 pneumonia meet the criteria for ARDS, there is some discussion about whether COVID-19 pneumonia is its own specific disease with atypical phenotypes. Anecdotal evidence from Italy and the US suggests that the main characteristic of the atypical presentation is the dissociation between well-preserved lung mechanics and the severity of hypoxaemia.[423] [424] [425] [426] [427] However, this approach has been criticised.[428] [429] It has been argued that an evidence-based approach extrapolating data from ARDS not related to COVID-19 is the most reasonable approach for intensive care of COVID-19 patients.[430]

As a consequence of this, some clinicians have warned that protocol-driven ventilator use may be causing lung injury in some patients, and that ventilator settings should be based on physiological findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.[423] NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[431] PEEP should always be carefully titrated and you should consult an intensivist with experience in treating COVID-19 patients for guidance.[394]

Consider prone ventilation for 12 to 16 hours per day in patients with persistent severe hypoxic failure.[2] [392] [3] [432] Longer durations may be feasible in some patients.[433] Pregnant women may benefit from being placed in the lateral decubitus position.[2] 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.[434] Two small case series found that many people tolerate the prone position while awake, breathing spontaneously, or receiving non-invasive ventilation. In the patients who tolerated it, improvement in oxygenation and a decrease in respiratory rate occurred.[435] [436]

A trial of an inhaled pulmonary vasodilator may be considered in adults who have severe acute respiratory distress syndrome and hypoxaemia despite optimising ventilation. However, this should be tapered off if there is no rapid improvement in oxygenation. Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[392] [3]

There has been some suggestion that lung injury due to COVID-19 may be similar to high-altitude pulmonary oedema (HAPO); however, there is no evidence to support this, and treatments used for HAPO (e.g., acetazolamide) should not be used for the treatment of COVID-19.[437]

**Severe COVID-19: extracorporeal membrane oxygenation**

There is insufficient evidence to recommend either for or against the routine use of extracorporeal membrane oxygenation (ECMO).[3] Some patients may require ECMO according to availability and expertise if the above methods fail.[2] [392] [432] [438] However, ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[439] Preliminary data on the use of ECMO in patients with COVID-19 is not promising, although it may play a useful role in salvaging select patients.[440] [441]

**Severe COVID-19: experimental therapies**

**Corticosteroids**
Corticosteroids are being used in some patients with COVID-19; however, they have been found to be ineffective and are not recommended.[27] [442] [443] A meta-analysis of over 5000 patients found that corticosteroid treatment in patients with COVID-19 was associated with longer hospital stays and a higher rate of mortality.[444] 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.[2]

The Infectious Diseases Society of America recommends against the use of corticosteroids in patients with COVID-19, except in the context of a clinical trial.[445] 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.[392] NIH guidelines say that there is insufficient evidence to recommend for or against the use of systemic corticosteroids in mechanically ventilated patients with acute respiratory distress syndrome.[3]

Other experimental therapies

- Drug therapies (e.g., antivirals) are being used in patients with COVID-19; however, unlicensed or experimental treatments should only be administered in the context of ethically-approved clinical trials.[2] See our Emerging section for more information about these treatments.

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

Patients with mild illness who have risk factors for poor outcomes (i.e., age >60 years, presence of comorbidities) should also be prioritised for hospital admission.[383] Patients with moderate illness (e.g., dyspnoea but blood oxygen saturation is at least 94%) are also usually hospitalised.[446] 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.[383]

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.[383]

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

- [WHO: home care for patients with COVID-19 presenting with mild symptoms and management of their contacts]
- [CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19)]
Recommend symptomatic therapies (as per the recommendations above) and advise patients to keep hydrated but not to take too much fluid as this can worsen oxygenation. Advise patients to improve air circulation by opening a window or door (fans can spread infection and should not be used).[390]

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

**Pregnancy and breastfeeding**

Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as mental health and psychosocial support. There is no evidence to suggest that pregnant women are more likely to contract COVID-19, or present with increased risk of severe illness or fetal compromise. Data on pregnant women with COVID-19 are limited; however, pregnant women can generally be treated with the same supportive therapies detailed above, taking into account the physiological changes that occur with pregnancy.[2] [447]

More than 15% of asymptomatic maternity patients tested positive for SARS-CoV-2 infection despite having been screened negative using a telephone screening tool in one small observational study in New York. In addition to this, 58% of their asymptomatic support persons tested positive despite being screened negative.[448] Another study in a New York obstetric population found that 88% of women who tested positive for SARS-CoV-2 at admission were asymptomatic at presentation.[449] The prevalence of asymptomatic SARS-CoV-2-positive pregnant women was lower (<3%) in a population in Connecticut.[450]

One in five pregnant women hospitalised with COVID-19 infection were admitted to the intensive care unit or required urgent delivery due to respiratory deterioration.[157]

**Location of care**

- Manage suspected and confirmed cases in a hospital setting with appropriate maternal and fetal monitoring whenever possible. Women with severe illness or complications may require admission to an intensive care unit. Consider home care in women with asymptomatic or mild illness, provided the patient has no signs of potentially severe illness (e.g., breathlessness, haemoptysis, new chest pain/pressure, anorexia, dehydration, confusion), no comorbidities, and no obstetric issues; the patient is able to care for herself; and monitoring and follow-up is possible.[283] [451] [452]
- The American College of Obstetricians and Gynecologists has published an algorithm to help decide whether hospital admission or home care is more appropriate. [ACOG: outpatient assessment and management for pregnant women with suspected or confirmed novel coronavirus (COVID-19)]

**Delivery**

- Choice of delivery and timing should be individualised based on gestational age, as well as maternal, fetal, and delivery conditions. Induction of labour and vaginal delivery is preferred in pregnant women with confirmed COVID-19 infection to avoid unnecessary surgical complications; however, an emergency caesarean delivery may be required if medically justified (e.g., in patients...
with complications such as sepsis or if there is fetal distress). A negative pressure isolation room is recommended in confirmed cases for labour, delivery, and neonatal care, if possible.[2] [283] [452] Birthing pools should be avoided in patients with suspected or confirmed infection.[453]

- Corticosteroid therapy may be considered in women who are at risk of preterm birth from 24 to 37 weeks’ gestation for fetal lung maturation, but caution is advised as this could potentially worsen the maternal clinical condition, and the decision should be made in conjunction with the multidisciplinary team.[2] [283] [452] [454] Corticosteroids for fetal lung maturation have not been shown to cause more harm in patients with COVID-19.[453]

Newborn care and breastfeeding

- Babies born to mothers with suspected or confirmed infection should be considered a person under investigation and tested at 24 hours and 48 hours after birth.[455]
- 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).[2] The CDC recommends that temporary separation of a newborn from a mother with confirmed or suspected COVID-19 should be strongly considered. However, the risks and benefits should be discussed with the mother and decisions made in accordance with the mother’s wishes. If separation is not undertaken, measures to minimise the risk of transmission should be implemented.[456] A mother with confirmed infection should be counselled to take all possible precautions to avoid transmission to the infant during breastfeeding (e.g., hand hygiene, wearing a cloth face covering). Expressed milk should be fed to the newborn by a healthy carer.[457] The Royal College of Obstetricians and Gynaecologists recommends that mothers with confirmed infection and healthy babies are kept together in the immediate postnatal period.[453] Separation appears to be the best option for mothers who are severely or critically ill.[283] Consult local guidelines for specific recommendations.
- After discharge, advise mothers with COVID-19 to practice prevention measures (e.g., distance, hand hygiene, respiratory hygiene/mask) for newborn care until they are afebrile for 72 hours without use of antipyretics and at least 7 days have passed since symptoms first appeared. A newborn with documented infection requires close outpatient follow-up after discharge.[455]

Rationing of medical resources

Rationing of medical resources may be required during the pandemic if healthcare infrastructures are overwhelmed. This raises many ethical questions on how to best triage patients to save the most lives. Recommendations have been suggested, but there is no clear international guidance on this issue as yet.[458] [459] [460] [461] [462]

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
<table>
<thead>
<tr>
<th>Initial</th>
<th>(summary)</th>
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<tbody>
<tr>
<td>suspected COVID-19</td>
<td>1st isolation and infection prevention and control procedures</td>
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<tr>
<td></td>
<td>plus monitoring</td>
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<td></td>
<td>adjunct empirical antimicrobials</td>
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<td>adjunct supportive care</td>
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<td></td>
<td>adjunct antipyretic</td>
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<td>adjunct antitussive</td>
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<tr>
<td>Acute confirmed COVID-19</td>
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<tr>
<td>moderate to severe illness; mild illness with risk factors</td>
<td>1st hospital admission</td>
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<td></td>
<td>plus infection prevention and control procedures</td>
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<td></td>
<td>plus treatment and care planning</td>
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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.
Coronavirus disease 2019 (COVID-19)  

TREATMENT  

Initial suspected COVID-19

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

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

» [BMJ: covid-19 - PPE guidance]

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

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

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

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

» Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as mental health and psychosocial support.[2] [452]

**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.[2]

**adjunct empirical antimicrobials**

Treatment recommended for SOME patients in selected patient group

» Consider starting empirical antimicrobials if there is clinical suspicion of bacterial infection. Do not wait for microbiology results. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-
Coronavirus disease 2019 (COVID-19) 

Treatment

Initial

risk criteria, or within 4 hours of establishing a diagnosis of pneumonia. Choice of empirical antimicrobials should be based on the clinical diagnosis, availability, and local epidemiology, resistance, and susceptibility data.[2] [362]

» Some guidelines recommend empirical antimicrobials for bacterial pathogens in all patients with community-acquired pneumonia without confirmed COVID-19. It is likely that the bacterial pathogens in patients with COVID-19 and pneumonia are the same as in previous patients with community-acquired pneumonia, and therefore empirical antimicrobial recommendations should be the same.[363]

» However, the National Institute for Health and Care Excellence in the UK recommends that it is reasonable not to start empirical antimicrobials if you are confident that the clinical features are typical for COVID-19.[362] There is insufficient evidence to recommend empirical broad-spectrum antimicrobials in the absence of another indication.[3]

» Consider treatment with a neuraminidase inhibitor until influenza is ruled out.[2]

adjunct supportive care

Treatment recommended for SOME patients in selected patient group

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

» Oxygen: give supplemental oxygen at a rate of 5 L/minute to patients with severe acute respiratory infection and respiratory distress, hypoxaemia, shock, or SpO₂ <90%. [2] [392]

Titrate flow rates to reach a target SpO₂ ≥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 SpO₂ 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.[2] Some guidelines recommend that SpO₂ should be maintained no higher than 96%. [392] Some locations may recommend different targets in order to support prioritisation of oxygen flow for the most severely ill patients in hospital. For example, NHS England recommends a target of 92% to 95% in adults in the first instance (or 90% to 94% if clinically appropriate).[393] Oxygen delivery in patients with severe hypoxaemia can be increased by using a non-rebreathing mask and prone positioning.[394]
## Initial

<table>
<thead>
<tr>
<th><strong>Initial</strong></th>
<th><strong>adjunct antipyretic</strong></th>
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<tr>
<td>- Intravenous fluids: manage fluids conservatively in adults and children with severe acute respiratory infection when there is no evidence of shock as aggressive fluid resuscitation may worsen oxygenation.[2]</td>
<td></td>
</tr>
<tr>
<td>- Acid-base or electrolyte abnormalities: correct any abnormalities, such as hyperglycaemia or metabolic acidosis, according to local protocols.[397]</td>
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### Primary options

<table>
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<th><strong>Primary options</strong></th>
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<td>- 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</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>- 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</td>
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</table>

- Guidelines recommend an antipyretic for the relief of fever.[2] [392] However, current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections.[401] If used, these drugs should only be taken when necessary while symptoms are present.

- Some clinicians have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen could worsen COVID-19 or have a negative impact on disease outcome based on anecdotal reports and the fact these drugs can mask symptoms of bacterial infections.[402] [403] There is currently no strong evidence to support this. The European Medicines Agency, the Food and Drug Administration, and the Commission of Human Medicines do not recommend avoiding NSAIDs in COVID-19 when clinically indicated.[404] [405] [406] [407] The WHO has confirmed that there is no evidence at present of severe adverse events in COVID-19 patients taking NSAIDs, or effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[408] The National Institute for Health and Care Excellence in the UK has updated its guidance to
Initial

recommend either paracetamol or ibuprofen for the treatment of fever; however, it recommends taking the lowest effective dose of ibuprofen for the shortest period needed to control symptoms.[390] [409]

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

adjunct antitussive

Treatment recommended for SOME patients in selected patient group

Primary options

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

Secondary options

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

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

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

» Consider short-term use of an oral opioid in adults if the cough is distressing to the patient. Codeine (linctus or tablet) is the preferred first-line option, with oral morphine solution reserved as a second-line option.[390]
## Acute confirmed COVID-19

<table>
<thead>
<tr>
<th>1st hospital admission</th>
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<tbody>
<tr>
<td>» 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.[2]</td>
</tr>
<tr>
<td>» Patients with mild illness who have risk factors for poor outcomes (i.e., age &gt;60 years, presence of comorbidities) should also be prioritised for hospital admission when possible.[383] Patients with moderate illness (e.g., dyspnoea but blood oxygen saturation is at least 94%) are also usually hospitalised.[446] Further management of these patients depends on the clinical presentation and not all of the treatments below will apply to these patients.</td>
</tr>
<tr>
<td>» Manage suspected and confirmed cases in pregnant women in a hospital setting with appropriate maternal and fetal monitoring whenever possible. Women with severe illness or complications may require admission to an intensive care unit.[283] [451] [452] 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.[2] [452]</td>
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<th>plus infection prevention and control procedures</th>
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<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td>» Immediately isolate all confirmed cases in an area separate from other patients, and implement appropriate infection prevention and control procedures.</td>
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<tr>
<td>» [BMJ: covid-19 - PPE guidance]</td>
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<tr>
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<td>» [WHO: infection prevention and control during health care when COVID-19 is suspected]</td>
</tr>
<tr>
<td>» [CDC: interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings]</td>
</tr>
</tbody>
</table>
### Acute

- COVID-19 is a notifiable disease; report all confirmed cases to your local health authorities.
- The WHO recommends that patients should remain in isolation for 2 weeks after symptoms disappear, and visitors should not be allowed until the end of this period. [463] Guidance on when to stop isolation depends on local circumstances and may differ between countries; consult local guidelines.

### Treatment and Care Planning

Treatment recommended for ALL patients in selected patient group

- Assess all adults for frailty on admission to hospital, irrespective of age and COVID-19 status, using the Clinical Frailty Scale. [391] [Clinical frailty scale]
- Discuss the risks, benefits, and potential outcomes of treatment options with patients and their families, and allow them to express preferences about their management. Take their wishes and expectations into account when considering the ceiling of treatment. Use decision support tools if available. Put treatment escalation plans in place, and discuss any existing advance care plans or advance decisions to refuse treatment with patients who have pre-existing advanced comorbidities. [390]
- Involve critical care teams in discussions about admission to critical care. [391]

### 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. [2]

### Supportive Care

Treatment recommended for SOME patients in selected patient group

- Immediately start supportive care, if necessary.
- Oxygen: give supplemental oxygen at a rate of 5 L/minute to patients with severe acute respiratory infection and respiratory distress, hypoxaemia, shock, or SpO₂ <90%. [2] [392] Titrate flow rates to reach a target SpO₂ ≥94%.
**Acute**

during resuscitation. Use a face mask with a reservoir bag (at 10-15 L/minute) if the patient is in critical condition. Once the patient is stable, the target SpO₂ 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. Some guidelines recommend that SpO₂ should be maintained no higher than 96%. Some locations may recommend different targets in order to support prioritisation of oxygen flow for the most severely ill patients in hospital. For example, NHS England recommends a target of 92% to 95% in adults in the first instance (or 90% to 94% if clinically appropriate). Oxygen delivery in patients with severe hypoxaemia can be increased by using a non-rebreathing mask and prone positioning.

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

- Managing breathlessness: keep the room cool, and encourage relaxation, breathing techniques, and changing body positions. Identify and treat any reversible causes of breathlessness (e.g., pulmonary oedema). Consider a trial of oxygen, if available. Consider an opioid and benzodiazepine combination in patients with moderate to severe breathlessness or patients who are distressed.

- Acid-base or electrolyte abnormalities: correct any abnormalities, such as hyperglycaemia or metabolic acidosis, according to local protocols.

- Managing anxiety, delirium, and agitation: identify and treat any reversible causes (e.g., offer reassurance, treat hypoxia). Consider a benzodiazepine for the management of anxiety or agitation. Consider haloperidol or a phenothiazine for the management of delirium. Non-pharmacological interventions are the mainstay for the management of delirium when possible, and prevention is key.

- Managing olfactory dysfunction: often improves spontaneously and does not require treatment. Consider treatment (e.g., olfactory training) if it persists beyond 2 weeks.

- Implement standard interventions to prevent complications associated with critical illness.
Acute

adjunct venous thromboembolism (VTE) prophylaxis
Treatment recommended for SOME patients in selected patient group

Primary options

» enoxaparin: consult specialist for guidance on dose

OR

» dalteparin: consult specialist for guidance on dose

OR

» fondaparinux: consult specialist for guidance on dose

Secondary options

» heparin: consult specialist for guidance on dose

» Start appropriate VTE prophylaxis in hospitalised adults with COVID-19 as per the standard of care for other hospitalised adults without COVID-19, provided there are no contraindications. A COVID-19 diagnosis should not influence a paediatrician’s recommendations about VTE prophylaxis in hospitalised children. Pregnant women should be managed by a specialist.[3] [398]

» Low molecular weight heparin or fondaparinux are preferred over unfractionated heparin in order to reduce patient contact. Unfractionated heparin is contraindicated in patients with severe thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia. Mechanical thromboprophylaxis is recommended if anticoagulation is contraindicated or is not available.[399]

» The optimal anticoagulant dose for VTE prophylaxis in COVID-19 patients is unknown. Some clinicians are using intermediate- or full-dose regimens rather than prophylactic doses as they are worried about undetected thrombi; however, this may lead to major bleeding events.[400] There are insufficient data to recommend increased anticoagulant doses for VTE prophylaxis in COVID-19 patients outside the setting of a clinical trial.[3] However, some
<table>
<thead>
<tr>
<th>Acute</th>
<th>guidelines recommend that escalated doses can be considered in critically ill patients.[398]</th>
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<tbody>
<tr>
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<td>» Routine post-discharge VTE prophylaxis is not recommended, except in certain high-risk patients.[3] [398]</td>
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<td>» There is little high-quality guidance for VTE prophylaxis in COVID-19 patients; therefore, clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[398]</td>
</tr>
<tr>
<td>adjunct empirical antimicrobials</td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td></td>
<td>» Reassess antimicrobial use daily, if started, in order to minimise the consequences of unnecessary antimicrobial therapy. De-escalate empirical therapy based on microbiology results and clinical judgement.[2]</td>
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<tr>
<td></td>
<td>» Some patients may require continued antimicrobial therapy once COVID-19 has been confirmed depending on the clinical circumstances (e.g., clinical or microbiological evidence of bacterial infection regardless of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] test results, SARS-CoV-2 test result is positive but clinical features are not typical for COVID-19).[362]</td>
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<td>» In these circumstances, review antibiotic choice based on microbiology results and switch to a narrower-spectrum antibiotic if appropriate, review intravenous antibiotic use within 48 hours and consider switching to oral therapy, and give for a total of 5 days unless there is a clear indication to continue.[362]</td>
</tr>
<tr>
<td>adjunct antipyretic</td>
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» Some clinicians have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen could worsen COVID-19 or have a negative impact on disease outcome based on anecdotal reports and the fact these drugs can mask symptoms of bacterial infections.[402] [403] There is currently no strong evidence to support this. The European Medicines Agency, the Food and Drug Administration, and the Commission of Human Medicines do not recommend avoiding NSAIDs in COVID-19 when clinically indicated.[404] [405] [406] [407] The WHO has confirmed that there is no evidence at present of severe adverse events in COVID-19 patients taking NSAIDs, or effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[408] The National Institute for Health and Care Excellence in the UK has updated its guidance to recommend either paracetamol or ibuprofen for the treatment of fever; however, it recommends taking the lowest effective dose of ibuprofen for the shortest period needed to control symptoms.[390] [409]

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

**adjunct antitussive**

Treatment recommended for SOME patients in selected patient group

**Primary options**

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

**Secondary options**

» morphine sulfate: adults: 2.5 to 5 mg orally every 4 hours when required initially, increase
### Acute

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<tr>
<td>»</td>
<td>Provide advanced oxygen/non-invasive ventilatory support in patients who are deteriorating and failing to respond to standard oxygen therapy, especially those with fatigue and at risk for exhaustion because of respiratory distress. [2]</td>
</tr>
<tr>
<td>»</td>
<td>These procedures may avoid the need for intubation and mechanical ventilation; however, they have a higher risk of aerosol generation. [417] Follow local infection prevention and control procedures to prevent transmission to healthcare workers, especially when performing aerosol-generating procedures.</td>
</tr>
<tr>
<td>»</td>
<td>Consider a trial of high-flow nasal oxygen or non-invasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in patients with hypoxaemic respiratory failure. [2] [392]</td>
</tr>
<tr>
<td>»</td>
<td>There is ongoing debate about the optimal mode of respiratory support before mechanical ventilation, and you should check local guidelines for preferred options. [418] NHS England recommends CPAP as the preferred form of non-invasive ventilation, and doesn't advocate the use of high-flow nasal oxygen based on a lack of efficacy, oxygen use, and infection spread. High-flow oxygen delivery can place a strain on oxygen supplies with the risk of site supply failure. Early CPAP may provide a bridge to invasive mechanical ventilation. Use of BiPAP should be reserved for patients with hypercapnic acute or chronic ventilatory failure. [419] The US National Institutes of Health recommends high-flow nasal oxygen for acute hypoxaemic respiratory failure over non-invasive...</td>
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</table>
Coronavirus disease 2019 (COVID-19)

**Treatment**

<table>
<thead>
<tr>
<th>Acute</th>
<th>adjunct</th>
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<tbody>
<tr>
<td>positive pressure ventilation, unless high-flow nasal oxygen is not available. [3]</td>
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</tr>
<tr>
<td>» Despite the trend to avoid high-flow nasal oxygen, it has been shown to have a similar risk of aerosol generation to standard oxygen masks. [420]</td>
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<tr>
<td>» Monitor patients closely for clinical deterioration that could result in the need for urgent intubation. [2] Patients with lower PaO₂/fraction of inspired oxygen (FiO₂) were more likely to experience failure with high-flow nasal oxygen and require ventilation in one study. [421]</td>
<td></td>
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<tr>
<td><strong>invasive mechanical ventilation</strong></td>
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<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td>» Consider intubation and mechanical ventilation in patients who are acutely deteriorating. [2]</td>
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</tr>
<tr>
<td>» Endotracheal intubation should be performed by an experienced provider using airborne precautions. Intubation by video laryngoscopy is recommended if possible. [3]</td>
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<tr>
<td>» Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require pre-oxygenation with 100% FiO₂ for 5 minutes. [2]</td>
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<tr>
<td>» The WHO, National Institutes of Health, and Surviving Sepsis Campaign guidelines recommend that mechanically ventilated patients with acute respiratory distress syndrome (ARDS) should receive a lung-protective, low tidal volume/low inspiratory pressure ventilation strategy (lower targets are recommended in children). A higher positive end-expiratory pressure (PEEP) strategy is preferred over a lower PEEP strategy. [2] [392] [3]</td>
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</table>
| » Although some patients with COVID-19 pneumonia meet the criteria for ARDS, there is some discussion about whether COVID-19 pneumonia is its own specific disease with atypical phenotypes. Anecdotal evidence from Italy and the US suggests that the main characteristic of the atypical presentation is the dissociation between well-preserved lung mechanics and the severity of hypoxaemia. [423] [424] [425] [426] [427] However, a small retrospective analysis found that this phenotyping schema does not accurately describe COVID-19 patients, and the features of the phenotypes are not mutually exclusive. [428] Experts argue that an evidence-
Coronavirus disease 2019 (COVID-19)

### Acute

**based approach extrapolating data from ARDS not related to COVID-19 is the most reasonable approach for intensive care of COVID-19 patients.**[430]

> As a consequence of this, some clinicians have warned that protocol-driven ventilator use may be causing lung injury in some patients, and that ventilator settings should be based on physiological findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.[423] NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[431] PEEP should always be carefully titrated and you should consult an intensivist with experience in treating COVID-19 patients for guidance.[394]

> Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[392] [3]

**adjunct prone positioning**

Treatment recommended for SOME patients in selected patient group

> Consider prone ventilation for 12 to 16 hours per day in patients with persistent severe hypoxic failure.[2] [392] [3] [432] Longer durations may be feasible in some patients.[433]

> Pregnant women may benefit from being placed in the lateral decubitus position.[2]

> 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.[434]

> Two small case series found that many people tolerate the prone position while awake, breathing spontaneously, or receiving non-invasive ventilation. In the patients who tolerated it, improvement in oxygenation and a decrease in respiratory rate occurred.[435] [436]

**adjunct inhaled pulmonary vasodilator**

Treatment recommended for SOME patients in selected patient group

> A trial of an inhaled pulmonary vasodilator may be considered in adults who have severe acute respiratory distress syndrome and hypoxaemia despite optimising ventilation. However, this should be tapered off if there is no rapid improvement in oxygenation.[392] [3]
### Acute

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>adjunct</strong> extracorporeal membrane oxygenation</td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td>» Some patients may require extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[2][392][432] However, ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[439]</td>
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<tr>
<td>» There is insufficient evidence to recommend either for or against the routine use of ECMO.[3] Preliminary data on the use of ECMO in patients with COVID-19 is not promising, although it may play a useful role in salvaging select patients.[440][441]</td>
<td></td>
</tr>
<tr>
<td><strong>adjunct</strong> experimental therapies</td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td>» 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.[2] See the Emerging section for more information about these treatments.</td>
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<tr>
<th>Condition</th>
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<tbody>
<tr>
<td><strong>mild illness with no risk factors</strong></td>
<td>1st isolation in non-traditional facility or at home</td>
</tr>
<tr>
<td>» Patients with mild illness and no risk factors (i.e., age &gt;60 years, presence of comorbidities) can be isolated in non-traditional facilities (e.g., repurposed hotels or stadiums) or at home when management in a healthcare facility is not possible. This will depend on guidance from local health authorities and available resources.[383] Forced quarantine orders are being used in some countries.</td>
<td></td>
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<tr>
<td>» 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.[383]</td>
<td></td>
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<tr>
<td>» Consider home care in pregnant women with asymptomatic or mild illness, provided the patient has no signs of potentially severe illness (e.g., breathlessness, haemoptysis, new chest pain/pressure, anorexia, dehydration, confusion), no comorbidities, and no obstetric issues; the</td>
<td></td>
</tr>
</tbody>
</table>
### Acute

- **TREATMENT**
  - 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. 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.

**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.
  - Advise patients to improve air circulation by opening a window or door (fans can spread infection and should not be used).
  - Olfactory dysfunction often improves spontaneously and does not require treatment. Consider treatment (e.g., olfactory training) if it persists beyond 2 weeks.

**adjunct antipyretic**

- Treatment recommended for SOME patients in selected patient group
### Treatment

**Acute**

<table>
<thead>
<tr>
<th><strong>Primary options</strong></th>
</tr>
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<tbody>
<tr>
<td>» 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</td>
</tr>
<tr>
<td>» 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</td>
</tr>
</tbody>
</table>

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

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

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

**Adjunct antitussive**

Treatment recommended for SOME patients in selected patient group

<table>
<thead>
<tr>
<th><strong>Primary options</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>» Ibuprofen is not recommended in pregnant women (especially in the third trimester) or children &lt;3 months of age (age cut-offs vary by country).</td>
</tr>
</tbody>
</table>
### Acute

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

### Secondary options

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

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

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

- Consider short-term use of an oral opioid in adults if the cough is distressing to the patient. Codeine (linctus or tablet) is the preferred first-line option, with oral morphine solution reserved as a second-line option.[390]
Emerging

Introduction

No treatments have been approved or shown to be safe and effective for the treatment of COVID-19, with the exception of remdesivir, which has been granted an emergency-use authorisation in the US. There are several treatments being used off-label (use of a licensed medication for an indication that has not been approved by a national drug regulatory authority), on a compassionate-use basis, or as part of a randomised controlled trial.[464] [465] [WHO: off-label use of medicines for COVID-19] It is important to note that there may be serious adverse effects associated with these drugs, and that these adverse effects may overlap with the clinical manifestations of COVID-19. These drugs may also increase the risk of death in an older patient or a patient with an underlying health condition. For example, chloroquine/hydroxychloroquine, azithromycin, oseltamivir, and lopinavir/ritonavir can all prolong the QT interval and are all potentially associated with an increased risk of cardiac death.[466] Drug-drug interactions with the patient’s existing medication(s) must also be considered (e.g., antivirals can interact with many drugs including direct oral anticoagulants). The World Health Organization (WHO) and its partners have launched the Solidarity trial, a large international study to compare four different treatments (local standard of care plus remdesivir, lopinavir/ritonavir, lopinavir/ritonavir plus interferon beta, or hydroxychloroquine/chloroquine) compared with local standard of care alone (which may include other experimental drug therapies as part of local standard of care).[467] [Global coronavirus COVID-19 clinical trial tracker]

Remdesivir

A novel, investigational, intravenous nucleoside analogue with broad antiviral activity that shows in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In the US, the Food and Drug Administration has issued an emergency-use authorisation for remdesivir for the treatment of suspected or confirmed COVID-19 in adults and children with hospitalised severe disease (defined as patients with low blood oxygen levels or needing oxygen therapy or more intensive breathing support such as a mechanical ventilator).[468] This authorisation is based on preliminary results from a randomised, placebo-controlled trial of remdesivir in 1063 patients hospitalised with severe COVID-19 run by the National Institute of Allergy and Infectious Disease (NIAID). The study found that patients taking a 10-day course of remdesivir had a faster time to recovery (i.e., defined as a patient no longer requiring hospitalisation, or hospitalisation no longer requiring oxygen or ongoing medical care) compared with placebo, with a median recovery time of 11 days versus 15 days. Results were significant only among patients who received oxygen. The mortality rate was 7.1% with remdesivir compared with 11.9% with placebo, although the difference was not statistically significant. The incidence of adverse effects was not significantly different between the two groups. Even though the trial was ongoing, the data and safety monitoring board made the recommendation to unblind the results to the trial team members from NIAID, who subsequently decided to make the results public.[469] The National Institutes of Health guidelines recommend remdesivir for the treatment of COVID-19 in hospitalised patients with severe disease, defined as SpO₂ ≤94% on ambient air (at sea level), requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation. The guidelines panel does not recommend remdesivir for the treatment of mild or moderate COVID-19 outside the setting of a clinical trial.[3] The manufacturer has issued a press release announcing preliminary findings from an open-label, phase 3 trial, reporting that a 5-day course is as safe and efficacious as a 10-day course.[470] Early results from one trial of patients treated with remdesivir on a compassionate-use basis indicated that approximately two-thirds of patients showed signs of clinical improvement (68% of patients had an improvement in oxygen support requirements); however, the study had no control arm and the majority of patients reported adverse effects.[471] A randomised, placebo-controlled trial in 240 hospitalised patients with severe COVID-19 in China found that remdesivir was not associated with significantly clinical benefits; however, the trial was underpowered, and while it showed some non-significant trends for benefit, it did not meet its primary end point.[472] It appears to be safe to use in pregnancy.[447] Possible adverse effects include elevated liver enzymes and infusion-related reactions (e.g., hypotension, nausea, vomiting, sweating, shivering). The European Medicines Agency has started a rolling review of remdesivir in order to speed up the assessment of this investigational drug for COVID-19 and has expanded its compassionate-use recommendations to include patients not on mechanical ventilation.[473] [474] The UK Medicines and Healthcare products Regulatory Agency has issued a positive opinion for the use of remdesivir as part of its COVID-19 Early Access to Medicines Scheme.[475]
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.[476] [477] They are being trialled in patients for the treatment of mild to severe COVID-19.[478] [479] [480] They are also being trialled for prevention and post-exposure prophylaxis in the healthcare setting.[481] [482] Initial data seemed promising, but more recent data show little to no effect with an increased risk of adverse events, although evidence is limited. A small randomised controlled trial found that hydroxychloroquine (with or without azithromycin) was efficient in reducing viral nasopharyngeal carriage of SARS-CoV-2 in 3 to 6 days in most patients.[483] However, this trial has been criticised for its limitations, and results from a similar trial could not replicate these findings.[484] [485] Another randomised trial in 62 patients in China found that hydroxychloroquine may shorten time to clinical recovery (in terms of resolution of fever and cough, and improvement of pneumonia on computed tomographic imaging); however, this study has not been peer reviewed as yet.[486] Early results from the largest randomised controlled trial completed so far of 150 people in China found that the overall 28-day negative conversion rate was not significantly different between patients who received hydroxychloroquine and those who received standard of care. However, addition of hydroxychloroquine led to more rapid normalisation of C-reactive protein levels and recovery of baseline lymphopenia, which may be important. The time to the alleviation of symptoms was shorter compared with standard of care in the subgroup of patients who did not receive antiviral treatment in the post-hoc analysis. The rate of adverse effects was higher in the hydroxychloroquine group (diarrhoea being the most common adverse effect). This study has not been peer reviewed yet and has several limitations (e.g., delay between symptom onset and starting treatment, inclusion of other antiviral therapies in the standard of care group).[487] According to an observational study of over 1400 hospitalised patients in New York, hydroxychloroquine was not associated with a reduced risk for intubation or death compared with those who did not receive hydroxychloroquine, and the authors conclude that further randomised controlled trials are needed.[488] Another observational study of 181 patients across four tertiary care centres in France found that in patients with severe COVID-19 who require oxygen, hydroxychloroquine appeared to have no effect on reducing admissions to intensive care or deaths at day 21 after hospital admission.[489] A multinational registry analysis of the use of hydroxychloroquine or chloroquine (with or without a macrolide antibiotic) found that the use of these regimens was independently associated with an increased risk of in-hospital mortality and ventricular arrhythmias.[490] However, the authors state that the association of decreased survival should be interpreted cautiously due to limitations of the study, and that randomised clinical trials are required before a conclusion regarding benefit or harm can be reached. Despite this, the WHO has temporarily paused the clinical trial arm testing hydroxychloroquine in the Solidarity trial based on this observational study. Hydroxychloroquine has similar therapeutic effects to chloroquine, but fewer adverse effects, is considered safe in pregnancy, and is more readily available in some countries.[491] Both drugs must be used with caution in patients with pre-existing cardiovascular disease due to the risk of arrhythmias.[492] Because chloroquine/hydroxychloroquine and azithromycin can both cause QT interval prolongation, caution is recommended when using these drugs together.[493] [494] The risk of QT interval prolongation and/or ventricular tachycardia (including Torsades de Pointes) is greater when these drugs are used in combination compared with the risk associated with either drug used alone (0.6% versus 1.5%).[495] A preprint study (not peer reviewed) found an increased risk of 30-day cardiovascular mortality when azithromycin was added to hydroxychloroquine in patients with COVID-19.[496] This combination is not recommended except in the context of a clinical trial.[3] Caution is recommended with the dosing regimen used for chloroquine due to the risk of chloroquine poisoning.[497] Higher doses of chloroquine have been associated with an increased risk of QT interval prolongation compared with lower doses, especially when used in combination with other drugs that prolong the QT interval.[498] Guidelines in China and Italy recommend these drugs for the treatment of COVID-19; however, this is based on weak evidence.[480] Surviving Sepsis Campaign and National Institutes of Health guidelines concluded that there is insufficient evidence to offer any recommendation on use of these drugs in the intensive care unit. However, the National Institutes of Health recommends against the use of high-dose chloroquine owing to an increased risk of toxicity.[392] [3] The American Thoracic Society recommends that either drug may be used on a case-by-case basis provided the patient’s condition is severe enough to warrant investigational therapy, the benefits and risks of treatment are discussed with the patient, data is collected on outcomes, and the drug is not in short supply.[432] The European Medicines Agency (EMA) has stressed that these drugs have not been shown to be effective in treating COVID-19 as yet, and should only be used in the context of clinical trials or emergency-use programmes.[499] In the US, the Food and Drug Administration (FDA) has granted an emergency-use authorisation for chloroquine and hydroxychloroquine to treat patients when a clinical
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.[503] A randomised controlled trial of 200 patients with severe disease found that treatment with lopinavir/ritonavir plus standard care (i.e., oxygen, non-invasive and invasive ventilation, antibiotics, vasopressors, renal replacement therapy, and extracorporeal membrane oxygenation, as necessary) was not associated with an decreased time to clinical improvement compared with standard care alone, and 28-day mortality was similar in both groups.[504] There is currently no strong evidence of efficacy of lopinavir/ritonavir in the treatment of COVID-19. Lopinavir/ritonavir (and other protease inhibitors) should only be used in the context of a clinical trial.[3] [Centre for Evidence-Based Medicine: lopinavir/ritonavir - a rapid review of effectiveness in COVID-19] Lopinavir/ritonavir is considered safe in pregnancy.[447]

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.[505] 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.[506] A systematic review of five studies found that convalescent plasma may reduce mortality in critically ill patients, have a beneficial effect on clinical symptoms, and reduce viral load.[507] In the US, the FDA is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of single patient emergency investigational new drug applications, and has issued guidance for its use. The FDA is encouraging patients who have recovered (complete resolution of symptoms for at least 2 weeks prior to donation; a negative reverse-transcription polymerase chain reaction [RT-PCR] test is not necessary to qualify for donation) to donate their plasma.[508] [509] [510] There is currently insufficient evidence to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.[3] The authors of a Cochrane rapid review were uncertain as to whether convalescent plasma is an effective treatment for COVID-19. The completed studies were of poor quality, and the results could be related to natural progression of the disease or to other treatments the patient receives.[511]

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.[512]

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is being trialled in some patients with COVID-19.[28] [513] Novel multi-antibody cocktail therapies are also in development for prophylaxis or treatment.[514] A retrospective study of 58 patients with severe COVID-19 found that IVIG, when used as an adjuvant treatment within 48 hours of admission, may reduce the use of mechanical ventilation, reduce hospital/intensive care unit stay, and reduce 28-day mortality; however, this study had several limitations.[515] There is currently insufficient evidence to recommend either for or against the use of IVIG for the treatment of COVID-19. The National Institutes of Health guidelines panel recommends against the use of non-SARS-CoV-2-specific IVIG for the treatment of COVID-19 except in the context of a clinical trial.[3]

Treatments for cytokine release syndrome
Interleukin-6 receptor antagonist monoclonal antibodies (e.g., tocilizumab, sarilumab, siltuximab) are being trialled in COVID-19 patients for the treatment of virus-induced cytokine release syndrome.[516] [517] [518] [519] [520] [521] [522] [523] Tocilizumab and sarilumab are already approved in some countries for the treatment of rheumatological conditions, siltuximab is approved in some countries for Castleman’s disease, and tocilizumab is approved in some countries for the treatment of chimeric antigen receptor (CAR) T-cell-induced severe or life-threatening cytokine release syndrome. However, the decision to suppress the immune system of a critically unwell patient with COVID-19 is a difficult one; the beneficial anti-inflammatory effects of anti-inflammatory drugs must be weighed against the possibly detrimental effects of impairment of immunity.[524] Other drugs currently in clinical trials for the treatment of COVID-19-associated cytokine release syndrome include anakinra (an interleukin-1 inhibitor), the Janus kinase inhibitors fedratinib and baricitinib, and the C-C chemokine receptor type 5 (CCR5) antagonist leronlimab.[525] [526] [527] [528] Addition of high-dose intravenous anakinra to non-invasive ventilation and standard care (which included hydroxychloroquine and lopinavir/ritonavir) in COVID-19 patients with moderate to severe acute respiratory distress syndrome and hyperinflammation was associated with a higher survival rate at 21 days in a small retrospective study.[529] There is currently insufficient evidence to recommend either for or against the use of interleukin-6 inhibitors or anakinra for the treatment of COVID-19. Janus kinase inhibitors should only be used in the context of a clinical trial.[3] The National Institute for Health and Care Excellence in the UK states that there is no evidence available to determine whether anakinra is effective, safe, or cost-effective for treating adults and children with secondary haemophagocytic lymphohistiocytosis triggered by SARS-CoV-2 or a similar coronavirus.[530]

**Bacille Calmette-Guerin (BCG) vaccine**

The BCG vaccine is being trialled in some countries for the prevention of COVID-19, including in healthcare workers. There is some evidence that BCG vaccination prevents other respiratory tract infections in children and older people mediated by induction of innate immune memory.[531] However, there is no evidence to support its use in COVID-19, and the WHO does not recommend it for the prevention of COVID-19.[532]

**Bemcentinib**

An experimental small molecule that inhibits AXL kinase. Bemcentinib has previously demonstrated a role in the treatment of cancer, but has also been reported to have antiviral activity in preclinical models, including activity against SARS-CoV-2. It is the first candidate to be selected as part of the UK’s Accelerating COVID-19 Research and Development (ACCORD) study. The multicentre, phase 2, adaptive randomisation platform trial aims to assess the safety and efficacy of multiple candidates.[533]

**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.[534] [535] [536] However, some experts believe that these drugs may worsen COVID-19 due to overexpression of ACE2 in people taking these drugs. See Management Approach for a discussion of the controversy.

**Other antivirals**

Various other antiviral drugs (monotherapy and combination therapy) are being trialled in patients with COVID-19 (e.g., oseltamivir, darunavir, ganciclovir, favipiravir, baloxavir marboxil, umifenovir, ribavirin, interferon).[537] [538] [539] [540] [541] [542] [543] [544] [545] Umifenovir monotherapy may be superior to lopinavir/ritonavir in treating COVID-19 in terms of reduced viral load and shorter duration of positive molecular tests.[546] Triple therapy with interferon beta-1b, lopinavir/ritonavir, and ribavirin has been tested in hospitalised COVID-19 patients in a small open-label randomised phase 2 trial. Patients who received triple therapy had a significantly shorter median time to a negative nasopharyngeal swab result compared with the control group (lopinavir/ritonavir only). Patients had mild to moderate disease at the time of enrollment.[547]

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

Vitamin D

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

Traditional Chinese medicine

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

Hyperbaric oxygen

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

Nitric oxide

Studies indicate that nitric oxide may help to reduce respiratory tract infection by inactivating viruses and inhibiting their replication in epithelial cells. The US Food and Drug Administration has approved an investigational drug application for inhaled nitric oxide to be studied in a phase 3 study of up to 500 patients with COVID-19. Other studies are currently recruiting.
**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. However, there are no data on the value of using these scores in patients with COVID-19 in the primary care setting.

Monitor coagulation parameters (e.g., D-dimer, fibrinogen, platelet count, prothrombin time) regularly (e.g., every 2-3 days) to identify worsening coagulopathy in hospitalised patients.

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. Perform fetal growth ultrasound 14 days after resolution of symptoms.

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

**Patient instructions**

**General prevention measures**

- Wash hands often with soap and water for at least 20 seconds or an alcohol-based hand sanitiser (that contains at least 60% alcohol), especially after being in a public place, blowing your nose, or coughing/sneezing. Avoid touching the eyes, nose, and mouth with unwashed hands.

- Avoid close contact with people (i.e., maintain a distance of at least 1 metre [3 feet]) including shaking hands, particularly those who are sick, have a fever, or are coughing or sneezing. It is important to note that recommended distances differ between countries (for example, 2 metres [6 feet] is recommended in the US and UK) and you should consult local guidance.

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

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

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

- The World Health Organization recommends that people with symptoms should wear a medical mask, self-isolate, and seek medical advice as soon as possible. Masks are also recommended for those caring for a sick person at home when in the same room. Use of a mask alone is insufficient to provide adequate protection, and they should be used in conjunction with other infection prevention and control measures such as frequent hand hygiene and social distancing. It
is important to wash your hands with soap and water (or an alcohol-based sanitiser) prior to putting on a face mask, and to remove it correctly. Used masks should be disposed of properly.[227] [231]

- The Centers for Disease Control and Prevention recommends that homemade cloth face coverings can be worn in public settings where social distancing measures are difficult to maintain (e.g., pharmacies, supermarkets), especially in areas where there is significant community transmission.[228]
- [Public Health England: how to wear and make a cloth face covering]
- [CDC: use of cloth face coverings to help slow the spread of COVID-19 (includes instructions on how to make masks)]

Travel advice

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

Pets

- At this time, there is no evidence that companion animals (including pets and other animals) play a significant role in the spread of COVID-19, and the risk of animals spreading COVID-19 to people is considered to be very low. There is no evidence that the virus can spread to people from the skin or fur of companion animals.[727]
- A very small number of pets have been reported to be infected with the virus after close contact with people with confirmed COVID-19; however, thousands of pets have been tested in the US with none testing positive. There is emerging evidence that cats and ferrets are highly susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, while dogs and other livestock have no or low susceptibility. A tiger tested positive in a zoo and two domestic pet cats tested positive in New York.[728] [729] [730] [731] Transmission between cats has also been reported.[732]
- Advise patients to limit their contact with their pets and other animals, especially while they are symptomatic. Advise people to not let pets interact with people or animals outside the household, and if a member of the household becomes unwell to isolate them from everyone else, including pets.[733]
- [CDC: coronavirus disease 2019 (COVID-19) – if you have pets]

Athletes and highly active people

- Advise asymptomatic patients who test positive not to exercise for 2 weeks after their test result, with slow resumption of activity under the guidance of a healthcare team. Advise mildly symptomatic patients who test positive not to exercise until 2 weeks after symptom resolution and only after a thorough cardiac evaluation. If the assessment is normal, slow resumption of activity under the guidance of a healthcare team can be considered with close monitoring for clinical deterioration.[734]

Resources
Coronavirus disease 2019 (COVID-19) Follow up

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

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>comorbidities</td>
<td>short term</td>
<td>high</td>
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<tr>
<td>Data on the management of comorbidities in patients with COVID-19 is evolving rapidly. Tailor the management of critical illness to the patient’s comorbidities (e.g., decide which chronic therapies should be continued and which therapies should be temporarily stopped, monitor for drug-drug interactions).[2] For more information, see the Best Practice topic: Management of coexisting conditions in the context of COVID-19.</td>
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<tr>
<td>acute respiratory distress syndrome (ARDS)</td>
<td>short term</td>
<td>high</td>
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<tr>
<td>Reported in 15% to 33% of patients in case series.[27] [28] [252] [253] [309]</td>
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<tr>
<td>Children can quickly progress to ARDS.[8]</td>
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<tr>
<td>Factors that increase the risk of developing ARDS and death include older age, neutrophilia, elevated lactate dehydrogenase levels, and elevated D-dimer levels.[616]</td>
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<tr>
<td>Lung transplant has been reported in a small number of cases in China as the sole therapy for end-stage pulmonary fibrosis related to ARDS in COVID-19 patients.[617]</td>
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<tr>
<td>venous thromboembolism</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Coagulopathy in COVID-19 has a prothrombotic character, which may explain reports of thromboembolic complications.[618] Patients may be predisposed to venous thromboembolism due to the direct effects of COVID-19, or the indirect effects of infection (e.g., severe inflammatory response, critical illness, traditional risk factors).[400]</td>
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<tr>
<td>Venous thromboembolism (pulmonary embolism or deep vein thrombosis) has been reported in 20% to 31% of patients with severe COVID-19 in the intensive care unit (including some patients who were on thromboprophylaxis), and may be associated with poor prognosis.[619] [620] [621] [622] [623] [624] [625] Other studies have reported higher rates of 46% to 85%.[626] [627] [628]</td>
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<tr>
<td>Patients with very high D-dimer levels have the greatest risk of thrombosis and may benefit from active monitoring.[354] [355] If venous thromboembolism is suspected, perform a computed tomographic angiography or ultrasound of the venous system of the lower extremities.[629]</td>
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<tr>
<td>Treat patients with a thromboembolic event (or who are highly suspected to have thromboembolic disease if imaging is not possible) with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19. There are currently insufficient data to recommend either for or against using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19. Patients who require extracorporeal membrane oxygenation or continuous renal replacement therapy, or who have thrombosis of catheters or extracorporeal filters, should be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19.[3]</td>
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<tr>
<td>A high incidence (14.7%) of asymptomatic deep vein thrombosis was reported in a cohort of patients with COVID-19 pneumonia.[630] An autopsy study of 12 patients revealed deep vein thrombosis in 58% of patients in whom venous thromboembolism was not suspected before death.[631] These studies highlight the importance of having a high suspicion for venous thromboembolism in patients who have signs of coagulopathy, including elevated D-dimer level.</td>
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<tr>
<td>While these patients are at higher risk of thrombotic events, they may also be at an elevated risk for bleeding. In a small retrospective study, 11% of patients at high risk of venous thromboembolism also had a high risk of bleeding.[632]</td>
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</tbody>
</table>
Complications

Antiphospholipid antibodies and lupus anticoagulant have been detected in a small number of patients. The presence of these antibodies can rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis. The significance of this finding is unknown, although it is thought that these antibodies may not be involved in the pathogenesis of venous thromboembolism in patients with severe COVID-19. [633] [634] [635]

It has been suggested that a new term (e.g., COVID-19-associated pulmonary thrombosis, diffuse pulmonary intravascular coagulopathy, or microvascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome [MicroCLOTS]) be used rather than the term pulmonary embolism as it has been hypothesised that the pathophysiology is different; local thrombi are formed in the lung vessels due to a local inflammatory process rather than the classical emboli coming from elsewhere in the body. [636] [637] [638]

Cases of arterial thrombosis, cerebral venous thrombosis, and acute limb ischaemia secondary to thrombosis have been reported. [639] [640] [641] [642] [643]

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>cardiovascular complications</td>
<td>short term</td>
<td>medium</td>
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COVID-19 is associated with a high inflammatory burden that can result in cardiovascular complications with a variety of clinical presentations. Inflammation in the vascular system can result in diffuse microangiopathy with thrombosis. Inflammation in the myocardium can result in myocarditis, heart failure, arrhythmias, acute coronary syndrome, rapid deterioration, and sudden death. [644] [645] [646] These complications can present on presentation or develop as the severity of illness worsens. [647]

It is uncertain to what extent acute systolic heart failure is mediated by myocarditis, cytokine storm, small vessel thrombotic complications, microvascular dysfunction, or a variant of stress-induced cardiomyopathy. [648]

Acute myocardial injury has been reported in 7% to 20% of patients in case series, and is indicated by elevated cardiac biomarkers. [27] [252] [309] [649] Acute myocardial injury at admission has been associated with a higher risk of all-cause mortality in patients with COVID-19. [650]

Prevalence of cardiac disease is high among patients who are severely or critically ill, and these patients usually require intensive care and have a poor prognosis and higher rate of in-hospital mortality. These patients are more likely to require non-invasive or invasive ventilation, and have a higher risk of thromboembolic events and septic shock compared with patients without a history of cardiac disease. [647] [649] [651] [652] [653] The mortality of patients with cardiovascular disease was 22% in one retrospective study, compared with the mortality of the overall population in the study, which was 9.8%. [654] Patients with underlying cardiovascular disease but without myocardial injury have a relatively favourable prognosis. [655]

Predictors for myocardial injury include older age, presence of cardiovascular-related comorbidities, and elevated C-reactive protein. Elevated myocardial markers predict risk for in-hospital mortality. [656]

Cases of fulminant myocarditis, cardiomyopathy, cardiac tamponade, myopericarditis with systolic dysfunction, pericarditis and pericardial effusion, ST-segment elevation (indicating potential acute myocardial infarction), cor pulmonale, and takotsubo syndrome have been reported. [9] [586] [589] [657] [658] [659] [660] [661]

Perform an ECG and order high-sensitivity troponin I (hs-cTnI) or T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients with symptoms or signs that suggest acute myocardial injury in order to make a diagnosis. Results should be considered in the clinical context. [662]

Monitor blood pressure, heart rate, and fluid balance, and perform continuous ECG monitoring in all patients with suspected or confirmed acute myocardial injury. [662]

There are limited data to recommend any specific drug treatments for these patients. Management should involve a multidisciplinary team including intensive care specialists, cardiologists, and infectious disease specialists.
Complications | Timeframe | Likelihood
--- | --- | ---
specialists.[648] It is important to consider that drugs such as hydroxychloroquine and azithromycin may prolong the QT interval and lead to arrhythmias.[662]
Guidelines for the management of COVID-19-related myocarditis are available.[663]
Infection may have longer-term implications for overall cardiovascular health; however, further research is required.[664]

| acute kidney injury | short term | medium |
--- | --- | ---
Overall risk in hospitalised patients is low, with a pooled incidence rate of 3%. This risk increases to 19% when patients are admitted to the intensive care unit.[665] In a retrospective study in New York, 35.6% of hospitalised patients went on to develop acute kidney injury, and of these 14.3% required renal replacement therapy. Nearly 90% of patients on mechanical ventilation developed acute kidney injury, and 97% of patients requiring renal replacement therapy were on ventilators.[666] Data from the UK indicate that approximately 31% of patients on ventilators (and 4% not on ventilators) require renal replacement therapy.[667] Similarly, 31% of critically ill patients in a New York study required dialysis.[143]
Can develop at any time before or during hospital admission. Risk factors include age ≥65 years, black ethnicity, history of acute kidney injury, chronic kidney disease, cardiovascular disease, hypertension, heart failure, hepatic disease, and diabetes.[666] [667] Causes include haemodynamic changes, hypovolaemia, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology, or rhabdomyolysis.[667] Direct kidney infection has been confirmed in an autopsy study of a single patient.[668]
Patients should meet criteria for acute kidney injury for diagnosis. [NHS England: acute kidney injury (AKI) algorithm] Perform a urinalysis for blood, protein, and glucose to help identify the underlying cause. Imaging is recommended if urinary tract obstruction is suspected.[667]
Stop any drugs that can cause or worsen acute kidney injury, if possible. Aim to achieve optimal fluid status (euvolaemia) in all patients. Consider a loop diuretic for treating fluid overload only. Manage hyperkalaemia according to local protocols. See local protocols for guidance on renal replacement therapy.[667]
Specialist input may be required in some cases (e.g., uncertainty about cause, abnormal urinalysis results, complex fluid management needs, indications for renal replacement therapy), and some patients may require critical care admission.[667]
Monitor fluid status daily, as well as serum urea, creatinine, and electrolytes at least every 48 hours (or more often if clinically indicated). Monitor patients for the development of, or progression to, chronic kidney disease for at least 2 to 3 years after acute kidney injury.[667]
Acute kidney injury is associated with poor prognosis.[666]
Cases of nephritis and collapsing glomerulopathy have been reported.[669] [670]

| acute liver injury | short term | medium |
--- | --- | ---
Abnormal liver function has been reported in 19% of patients. Patients in Hubei province were more likely to present with abnormal liver function compared with those outside of Hubei.[320]
Abnormal liver function (higher levels of aspartate aminotransferase, alanine aminotransferase, and total bilirubin, and lower levels of serum albumin) is associated with a significant increase in the severity of COVID-19 infection.[671] Although data support a higher prevalence of abnormal aminotransferase levels in patients with severe illness, evidence suggests that clinically significant liver injury is uncommon.[672]
Medications (e.g., lopinavir/ritonavir) may have a detrimental effect on liver injury.
### Complications

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<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>neurological complications</td>
<td>short term</td>
<td>medium</td>
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</table>

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

In a case series of 214 patients, neurological symptoms were seen in 36% of patients, and were more common in patients with severe illness.[673] In a small retrospective study of patients in an intensive care unit, 44% of patients with neurological symptoms had abnormal findings on brain magnetic resonance imaging.[674]

Complications include acute cerebrovascular disease (including large-vessel stroke in younger patients), impairment of consciousness, ataxia, seizures, neuralgia, skeletal muscle injury, corticospinal tract signs, meningitis, encephalitis, encephalopathy, myoclonus, and Guillain-Barre syndrome. Patients may present with these signs/symptoms, or they may develop them during the course of the disease. These patients have a poor prognosis.[675] [676] [677] [678]

Ischaemic stroke (confirmed on imaging) was reported in 0.9% of patients in a retrospective cohort study of hospitalised patients with COVID-19 in New York. Most strokes were cryptogenic.[679]

Guidelines for the management of acute ischaemic stroke in patients with COVID-19 infection have been published.[680]

| cytokine release syndrome     | short term | low        |

Cytokine release syndrome may cause ARDS or multiple-organ dysfunction, which may lead to death.[681] Elevated serum proinflammatory cytokines (e.g., tumour necrosis factor alpha, interleukin-2, interleukin-6, interleukin-8, interleukin-10, granulocyte-colony stimulating factor, monocyte chemoattractant protein 1) and inflammatory markers (e.g., C-reactive protein, serum ferritin) have been commonly reported in patients with severe COVID-19. This likely represents a type of virus-induced secondary haemophagocytic lymphohistiocytosis, which may be fatal.[27] [364] [594] [682] Interleukin-6, in particular, has been associated with severe COVID-19 and increased mortality.[596]

One study found that patients who require admission to the intensive care unit have significantly higher levels of interleukin-6, interleukin-10, and tumour necrosis factor alpha, and fewer CD4+ and CD8+ T cells.[683]

Anti-inflammatory/immunosuppressive treatments (e.g., tocilizumab, hydroxychloroquine/chloroquine, Janus kinase inhibitors) are being trialled in COVID-19 patients.[684] See our Emerging section for more information.

Cytokine release syndrome has been reported in children, although cases appear to be rare.[685] See section below on paediatric multisystem inflammatory syndrome.

| paediatric multisystem inflammatory syndrome | short term | low |

Also known as multisystem inflammatory syndrome in children (MIS-C).

A small number of children and adolescents who develop a significant systemic inflammatory response have been identified in some locations including Europe and the US. A small number of deaths have been reported.[686]

The rare syndrome shares common features with Kawasaki disease, toxic shock syndrome, bacterial meningitis, and macrophage activation syndromes. Common features include abdominal pain, other gastrointestinal symptoms, and cardiac inflammation (elevated troponin and pro-B-type natriuretic peptide
Complications

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<tr>
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<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>septic shock</td>
<td>short term</td>
<td>low</td>
</tr>
<tr>
<td>disseminated intravascular coagulation</td>
<td>short term</td>
<td>low</td>
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</table>

Reported in 4% to 8% of patients in case series.[27] [28] [252] [309]

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.[392] [3] Dopamine is only recommended as an alternative vasopressor in certain patients (e.g., those with a low risk of bradycardia or tachyarrhythmias). Dobutamine is recommended in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressors. Low-dose corticosteroid therapy is recommended for refractory shock.[3]

Reported in 71% of non-survivors.[696] Disseminated intravascular coagulation (DIC) is a manifestation of coagulation failure, and an intermediate link in the development of multi-organ failure. Patients may be at high risk of bleeding/haemorrhage or venous thromboembolism.[697]

Coagulopathy manifests as elevated fibrinogen, elevated D-dimer, and minimal change in prothrombin time, partial thromboplastin time, and platelet count in the early stages of infection. Increasing interleukin-6 levels correlate with increasing fibrinogen levels. Coagulopathy appears to be related to severity of illness and the resultant thromboinflammation. Monitor D-dimer level closely.[698]

Prophylactic-dose low molecular weight heparin should be considered in all hospitalised patients with COVID-19 (including those who are not critically ill), unless there are contraindications. This will also protect against venous thromboembolism.[699] 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.[700]
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<tr>
<th>Complications</th>
<th>Timeframe</th>
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<tr>
<td>In patients with heparin-induced thrombocytopenia (or a history of it), argatroban or bivalirudin are recommended.[697]</td>
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<tr>
<td>Standard guidance for the management of bleeding manifestations associated with DIC or septic coagulopathy should be followed if bleeding occurs; however, bleeding manifestations without other associated factors is rare.[698] [699]</td>
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<tr>
<td><strong>acute respiratory failure</strong></td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Reported in 8% of patients in case series.[28]</td>
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<tr>
<td>Leading cause of mortality in patients with COVID-19.[589]</td>
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<tr>
<td>Children can quickly progress to respiratory failure.[8]</td>
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<tr>
<td><strong>pregnancy-related complications</strong></td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Retrospective reviews of pregnant women with COVID-19 found that women appeared to have fewer adverse maternal and neonatal complications and outcomes than would be expected for those with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). Adverse effects on the newborn including fetal distress, premature labour, respiratory distress, thrombocytopenia, and abnormal liver function have been reported; however, it is unclear whether these effects are related to maternal SARS-CoV-2 infection. Maternal deaths have been reported, as well as miscarriage (including a case in the second trimester), ectopic pregnancy, intrauterine growth restriction, oligohydramnios, perinatal death, preterm birth, and neonatal death. It is unclear whether this is related to COVID-19.[100] [701] [447] [702] [703] [704] [705] [706] [707] [708] [709]</td>
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<tr>
<td><strong>secondary infection</strong></td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Reported in 6% to 10% of patients in case series.[27] [309]</td>
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<tr>
<td>Cases of <em>Staphylococcus aureus</em> superinfection and <em>Mycoplasma pneumoniae</em> have been reported.[710] [711]</td>
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<tr>
<td><strong>aspergillosis</strong></td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Invasive pulmonary aspergillosis has been reported in critically ill patients with moderate to severe ARDS.[712] [713] [714] A prospective observational study found that one third of mechanically ventilated patients with COVID-19 had putative invasive pulmonary aspergillosis.[715]</td>
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<tr>
<td>Intubation for more than 7 days may be a risk factor. Potential contributing factors include immunosuppression, critical illness, or use of high-dose corticosteroids. Consider aspergillosis in patients who deteriorate despite optimal supportive care or have other suspicious radiological or clinical features.[431]</td>
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<tr>
<td>Prescribe appropriate antifungal therapy according to local guidelines.[716]</td>
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<tr>
<td><strong>pancreatic injury</strong></td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Mild pancreatic injury (defined as elevated serum amylase or lipase levels) has been reported in 17% of patients in one case series. It is unknown whether this is a direct viral effect or due to the harmful immune response that occurs in some patients. Further research is required.[717]</td>
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<tr>
<td><strong>rhabdomyolysis</strong></td>
<td>short term</td>
<td>low</td>
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</table>
Complications | Timeframe | Likelihood
---|---|---
There have been case reports of rhabdomyolysis in adults and children.[718] [719]

**autoimmune haemolytic anaemia** | short term | low

Warm or cold autoimmune haemolytic anaemia (first episode) has been reported in 7 patients after the onset of COVID-19 symptoms and within the timeframe compatible with cytokine release syndrome. Four patients had indolent B lymphoid malignancy. It is unknown whether the haemolytic anaemia is related to COVID-19 infection.[720]

**immune thrombocytopenia** | short term | low

A small number of cases of immune thrombocytopenia have been reported in patients with COVID-19, including one case report in a 10-year-old child and another in a pregnant woman.[721] [722] [723]

**subacute thyroiditis** | short term | low

The first known case of subacute thyroiditis has been reported in an 18-year-old woman after SARS-CoV-2 infection. Subacute thyroiditis is a thyroid disease of viral or post-viral origin.[724]

### Prognosis

#### Case fatality rate

The overall global case fatality rate (CFR), defined as the total number of deaths reported divided by the total number of infections reported, is currently estimated to be 6.3% based on World Health Organization data as of 26 May 2020. The CFR varies considerably between countries; for example, it is currently higher in countries such as the UK, France, Italy, and Spain, and significantly lower in countries such as Russia, the US, Germany, Australia, Turkey, Iceland, and Singapore.[568]

The overall CFR in China has been estimated to be 2.3% (0.9% in patients without comorbidities) based on a large case series of 72,314 reported cases from 31 December 2019 to 11 February 2020 (mainly among hospitalised patients).[4] However, another study estimates the CFR in China to be lower at 1.38% (after adjusting the crude estimate for censoring, demography, and under-ascertainment).[569]

These figures need to be interpreted with extreme caution. In pandemics, CFRs tend to start high and then trend downwards as more data becomes available. For example, at the start of the 2009 H1N1 influenza pandemic the CFR varied from 0.1% to 5.1% (depending on the country), but the mortality rate ended up being around 0.02%.[570]  
[Centre for Evidence-Based Medicine: global COVID-19 case fatality rates]

Factors that affect the CFR include:

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

It is important to note that daily death counts need to be interpreted with caution. The number of deaths reported on a particular day may not accurately reflect the number of deaths from the previous day due to
delays associated with reporting deaths. This makes it difficult to know whether deaths are falling over time in the short term.[571]

In Italy, the CFR may be higher because Italy has the second oldest population in the world, the highest rates of antibiotic resistance deaths in Europe, and a higher incidence of smoking (a known risk factor for more severe disease). The way COVID-19 related deaths are identified and reported in Italy may have also resulted in an overestimation of cases. Patients who die ‘with’ COVID-19 and patients who die ‘from’ COVID-19 are both counted towards the death toll. Only 12% of death certificates have shown direct causality from COVID-19, while 88% of patients who have died had at least one comorbidity.[570] [572]

The overall CFR appears to be less than that reported for severe acute respiratory syndrome coronavirus (SARS) (10%) and Middle East respiratory syndrome (MERS) (37%).[27] Despite the lower CFR, COVID-19 has so far resulted in more deaths than both SARS and MERS combined.[573]

**Infection fatality rate**

The infection fatality rate (IFR) is the proportion of deaths among all infected individuals including confirmed cases, undiagnosed cases (e.g., mildly symptomatic or asymptomatic cases), and unreported cases. While the CFR is subject to selection bias as more severe/hospitalised cases are tested, the IFR gives a more accurate picture of the lethality of a disease, especially as testing becomes more rigorous within a population.

Among people on board the Diamond Princess cruise ship, a unique situation where an accurate assessment of the IFR in a quarantined population can be made, the IFR was 0.85%. However, all deaths occurred in patients >70 years of age, and the rate in a younger, healthier population could be much lower.[574]

Evidence is now emerging from seroprevalence studies that the prevalence of infections is much higher than the official figures suggest, and that the virus is much less lethal than the current global case and death counts indicate (0.08% to 0.5%). However, these studies have not been peer reviewed as yet, and may have limitations. Nevertheless, these studies indicate that the IFR may be much lower than the current CFRs.

- Iran: the seroprevalence estimate after adjusting for population and test performance characteristics in Guilan province was 22% to 33%, resulting in an estimated IFR of 0.08% to 0.12%.[575]
- Denmark: a seroprevalence study in blood donors estimates the IFR to be approximately 0.08% in people aged under 70 years.[576]
- New York: based on results of the first round of testing, a research team estimates that approximately 13.9% of the county’s adult population has antibodies to the virus, an estimated IFR of 0.5% based on current deaths in the county.[577]
- Los Angeles county, California: based on results of the first round of testing, a research team estimates that approximately 2.8% to 5.6% of the county’s adult population has antibodies to the virus, an estimated IFR of 0.1% to 0.2% based on current deaths in the county.[578] Published seroprevalence data from adults in Los Angeles county found that the community prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies was 4.65% in early April. Based on this figure, the authors estimate that approximately 367,000 county residents had SARS-CoV-2 antibodies. This is much higher than the number of confirmed infections at this time, which was 8430. They conclude that fatality rates based on the number of confirmed cases may be much higher than the rates based on the actual number of infections.[579]
- Santa Clara county, California: an analysis of 3300 people in early April found that the seroprevalence of antibodies to SARS-CoV-2 in Santa Clara county was between 2.49% and 4.16%. Based on this, researchers estimate that between 48,000 and 81,000 people were infected with the virus at the time (out of the county’s population of approximately 2 million people). Researchers estimate an IFR of 0.1% to 0.2% based on this data.[580]
- Germany: the overall seroprevalence in healthcare workers in a tertiary hospital was low (1.6%).[581]
- Iceland: the country where the most testing per capita has occurred - the IFR lies between 0.01% and 0.19%.[570]

These estimates are likely to change as more data emerge.
The Centers for Disease Control and Prevention’s current best estimate of the overall CFR in symptomatic cases is 0.4%. It projects a 35% rate of asymptomatic cases among those infected, which makes the IFR approximately 0.26%.[582]

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

The CFR increases with age.[569] 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.[583]

The majority of deaths in China have been in patients aged 60 years and older and/or those who have pre-existing underlying health conditions (e.g., hypertension, diabetes, cardiovascular disease). The CFR was highest among critical cases (49%). It was also higher in patients aged 80 years and older (15%), males (2.8% versus 1.7% for females), and patients with comorbidities (10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6% for hypertension, and 5.6% for cancer).[4] Another study found the CFR in China to be 6.4% in patients aged ≥60 years versus 0.32% in patients aged <60 years, and 13.4% in patients aged ≥80 years.[569]

In Italy, the CFR was 8.5% in patients aged 60 to 69 years, 35.5% in patients aged 70 to 79 years, and 52.5% in patients aged ≥80 years.[584] In a case series of 1591 critically ill patients in Lombardy, the majority of patients were older men, a large proportion required mechanical ventilation and high levels of positive end-expiratory pressure, and the mortality rate in the intensive care unit was 26%.[585]

In the US, the CFR was highest among patients aged ≥85 years (10% to 27%), followed by those aged 65 to 84 years (3% to 11%), 55 to 64 years (1% to 3%), 20 to 54 years (<1%), and ≤19 years (no deaths). Patients aged ≥65 years accounted for 80% of deaths.[7] The CFR among critically ill patients admitted to the intensive care unit reached 67% in one hospital in Washington state. Most of these patients had underlying health conditions, with congestive heart failure and chronic kidney disease being the most common.[586] The CFR in residents in a long-term care facility in Washington was reported to be 34%.[587]

The case fatality rate in patients with cancer was 37% for patients with haematological malignancies and 25% for solid malignancies in one study. Some 55% of lung cancer patients died from COVID-19.[588]

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

**Prognostic factors**

The leading cause of death in patients with COVID-19 is respiratory failure from acute respiratory distress syndrome.[589] Patients who required invasive mechanical ventilation had an 88% mortality rate in one study in New York, and a 53% mortality rate in one study in the UK.[146] [147] The other most common complications in deceased patients are myocardial injury, liver or kidney injury, and multi-organ dysfunction.[590] The strongest predictor of in-hospital mortality was chronic pulmonary disease, followed by chronic cardiovascular disease, older age, and elevated interleukin-6 and D-dimer levels at admission in a New York study.[143] 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.[591]

Prognostic factors that have been associated with disease progression to severe or critical illness or even death include:[108] [139] [147] [164] [348] [592] [593] [594] [595] [596] [597] [598] [599] [600]

- Age ≥65 years
- Male sex
- Smoking
- Presence of comorbidities (e.g., hypertension, diabetes, cardiovascular or cerebrovascular disease, respiratory disease, obesity)
- Dyspnoea
- Hypoxaemia
- Lymphopenia
- Leukocytosis
Follow up

- Thrombocytopenia
- High neutrophil-to-lymphocyte ratio
- Decreased albumin level
- Hyperglycaemia
- Liver or kidney impairment
- Elevated lactate dehydrogenase
- Elevated inflammatory markers (C-reactive protein, procalcitonin)
- Elevated cardiac troponin I
- Elevated D-dimer
- Elevated serum amyloid A
- Decreased CD3+, CD4+, or CD8+ T cells
- Elevated interleukin-6
- Higher Sequential Organ Failure Assessment (SOFA) or Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

Prognostic scores

The APACHE II score was found to be an effective clinical tool to predict hospital mortality in patients with COVID-19, and performed better than SOFA and CURB-65 scores in a small retrospective observational study. An APACHE II score of 17 or more was an early indicator of death and may help provide guidance to make further clinical decisions.[598] Further research is required to confirm these findings, and to validate the use of prognostic scores in patients with COVID-19.

New clinical risk scores to predict disease progression and the risk for critical illness in hospitalised patients with COVID-19 have been developed (e.g., COVID-GRAM, CALL score).[601] COVID-GRAM, a web-based calculator to estimate the probability that a patient will develop critical illness (defined as intensive care admission, invasive ventilation, or death) has been validated in a study of nearly 1600 patients in China. It relies on the following 10 variables at admission: chest radiographic abnormality, age, haemoptysis, dyspnoea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin. Additional validation studies, especially outside of China, are required.[602]

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.[603]

Infectivity of recovered cases

Potential infectivity of recovered cases is still unclear. There have been case reports of patients testing positive again after being discharged (i.e., after symptom resolution and two consecutive negative test results two days apart). This suggests that some patients in convalescence may still be contagious, although this is yet to be confirmed.[604] [605]

Reinfection/reactivation

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection/reactivation has been reported in patients after hospital discharge. These patients return a positive reverse-transcription polymerase chain reaction (RT-PCR) test again after two negative RT-PCR tests and after hospital discharge.[606] [607] [608] [609] [610] It is unclear whether these cases are reinfections/relapses/reactivations, or whether the test result was a false-negative at the time of discharge. It has been suggested that retesting positive may be due to discontinuing antiviral treatment in one patient.[611] In a small cross-sectional study, 10 out of 60 patients
had a positive RT-PCR from 4 to 24 days after index hospital discharge, presumed to be due to persistent viral shedding rather than reinfection.[612] Further research is required.

**Post-infection immunity**

Most convalescent patients have detectable neutralising antibodies and cellular immune responses.[613] A study in macaques suggests that infection with SARS-CoV-2 offers protection against reinfection.[614] There are no good data available yet on whether patients have immunity from reinfection after recovery. However, the limited data available suggest that recovery from COVID-19 might confer immunity against reinfection.[615]
# Diagnostic guidelines

## Europe

**COVID-19: guidance for health professionals**

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

**COVID-19**

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

## International

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

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

**Laboratory testing strategy recommendations for COVID-19**

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

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

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

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

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

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

**Published by:** World Health Organization  
**Last published:** 2020
### North America

**Information for laboratories about coronavirus (COVID-19)**

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

**Interim guidelines for COVID-19 antibody testing**

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

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

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

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

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

**COVID-19 resource center**

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

### Asia

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

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

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

Published by: Peking Union Medical College Hospital  
Last published: 2020
## Treatment guidelines

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**Recommendations for COVID-19 clinical management**

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<td><strong>ISTH interim guidance on recognition and management of coagulopathy in COVID-19</strong></td>
<td>International Society of Thrombosis and Haemostasis</td>
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<td><strong>Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19)</strong></td>
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<td><strong>Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the Anticoagulation Forum</strong></td>
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### North America

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

*Published by:* Centers for Disease Control and Prevention  
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**Management of infants born to mothers with COVID-19**

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

**Novel coronavirus 2019 (COVID-19)**

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

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

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

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

**Handbook of COVID-19 prevention and treatment**
*Published by:* First Affiliated Hospital, Zhejiang University School of Medicine  
*Last published:* 2020

**A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia**
*Published by:* Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team; Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care  
*Last published:* 2020

**Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7)**
*Published by:* National Health Commission of the People's Republic of China; National Administration of Traditional Chinese Medicine of the People's Republic of China  
*Last published:* 2020

**Diagnosis and clinical management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection**
*Published by:* Peking Union Medical College Hospital  
*Last published:* 2020

**Updates on COVID-19 (coronavirus disease 2019) local situation**
*Published by:* Ministry of Health Singapore  
*Last published:* 2020

**New coronavirus (COVID-19)#**
*Published by:* National Institute of Infectious Diseases Japan  
*Last published:* 2020

### 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](https://coronavirus.jhu.edu/))
2. BMJ talk medicine podcast: Covid-19 update ([external link](https://www.bmj.com/content/10.1136/bmj.m1058))
3. BMJ Best Practice: Management of co-existing conditions in the context of COVID-19 ([external link](https://bestpractice.bmj.com/))
7. CDC: COVIDView ([external link](https://www.cdc.gov/coronavirus/2019-ncov/cases-in-us.html))
11. CDC: strategies to optimize the supply of PPE and equipment ([external link](https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-supply-optimization.html))
12. BMJ: covid-19 - PPE guidance ([external link](https://www.bmj.com/content/10.1136/bmj.m1058))
13. BMJ: covid-19 in primary care (UK) ([external link](https://www.bmj.com/content/368/bmj.m1058))
14. BMJ: covid-19 - a remote assessment in primary care ([external link](https://www.bmj.com/content/368/bmj.m1058))
15. BMJ Learning: Covid-19 - handwashing technique and PPE videos ([external link](https://www.bmj.com/content/10.1136/bmj.m1058))
17. BMJ: facemasks for the prevention of infection in healthcare and community settings ([external link](https://www.bmj.com/content/10.1136/bmj.m1058))
18. BMJ: analysis - face masks for the public during the covid-19 crisis ([external link](https://www.bmj.com/content/10.1136/bmj.m1058))
22. BSTI: radiology decision tool for suspected COVID-19 ([external link](https://bestpractice.bmj.com/))
<p>| 23. | BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas (external link) |
| 24. | WHO: global surveillance for COVID-19 caused by human infection with COVID-19 virus (external link) |
| 25. | CDC: evaluating and testing persons for coronavirus disease 2019 (COVID-19) (external link) |
| 26. | CDC: priorities for testing patients with suspected COVID-19 infection (external link) |
| 27. | IDSA: COVID-19 prioritization of diagnostic testing (external link) |
| 28. | Clinical frailty scale (external link) |
| 29. | WHO: home care for patients with COVID-19 presenting with mild symptoms and management of their contacts (external link) |
| 30. | CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19) (external link) |
| 31. | ACOG: outpatient assessment and management for pregnant women with suspected or confirmed novel coronavirus (COVID-19) (external link) |
| 32. | WHO: off-label use of medicines for COVID-19 (external link) |
| 33. | Global coronavirus COVID-19 clinical trial tracker (external link) |
| 34. | Centre for Evidence-Based Medicine: hydroxychloroquine for COVID-19 - what do the clinical trials tell us? (external link) |
| 35. | Centre for Evidence-Based Medicine: lopinavir/ritonavir - a rapid review of effectiveness in COVID-19 (external link) |
| 36. | Centre for Evidence-Based Medicine: global COVID-19 case fatality rates (external link) |
| 37. | NHS England: acute kidney injury (AKI) algorithm (external link) |
| 38. | Public Health England: how to wear and make a cloth face covering (external link) |
| 39. | CDC: use of cloth face coverings to help slow the spread of COVID-19 (includes instructions on how to make masks) (external link) |
| 40. | WHO: coronavirus disease (COVID-19) travel advice (external link) |
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Figure 1: Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically

Centers for Disease Control and Prevention
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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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK
Contributors:

// Authors:

Nicholas J. Beeching, MA, BM BCh, FRCP, FRACP, FFTM RCPS (Glasg), FESCMID, DCH, DTM&H
Consultant and Honorary Senior Lecturer in Infectious Diseases
Royal Liverpool University Hospital and Liverpool School of Tropical Medicine, Liverpool, UK
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Tom E. Fletcher, MBE, PhD, MBChB, MRCP, DTM&H
Senior Clinical Lecturer and Defence Consultant in Infectious Diseases
Royal Liverpool University Hospital and Liverpool School of Tropical Medicine, Liverpool, UK
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Robert Fowler, MDCM, MS (Epi), FRCP(C)
H. Barrie Fairley Professor of Critical Care
University Health Network and Interdepartmental Division of Critical Care Medicine, Director, Clinical Epidemiology and Health Care Research, Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Chief, Tory Trauma Program, Sunnybrook Hospital, Toronto, Canada
DISCLOSURES: RF declares that he has no competing interests.

// Peer Reviewers:

William A. Petri, Jr., MD, PhD
Professor
Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, VA
DISCLOSURES: WAP declares that he has no competing interests.

Xin Zhang, MD, PhD
Attending Physician
The Fifth Medical Center of PLA General Hospital, Clinical Division and Research Center of Infectious Disease, Beijing, China
DISCLOSURES: XZ declares that he has no competing interests.

Ran Nir-Paz, MD
Associate Professor in Medicine
Department of Clinical Microbiology and Infectious Diseases, Hadassah Hebrew University Medical Center, Jerusalem, Israel
DISCLOSURES: RNP has received research grants from US-Israel Binational Science Foundation, Hebrew University, Rosetrees Trust, and SpeeDx. He is chair of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Mycoplasma and Chlamydia Infections (ESGMAC). RNP is a consultant for and has stocks in eDAS Healthcare. He is also chairperson of the Israeli Society for Infectious Diseases guidelines committee.