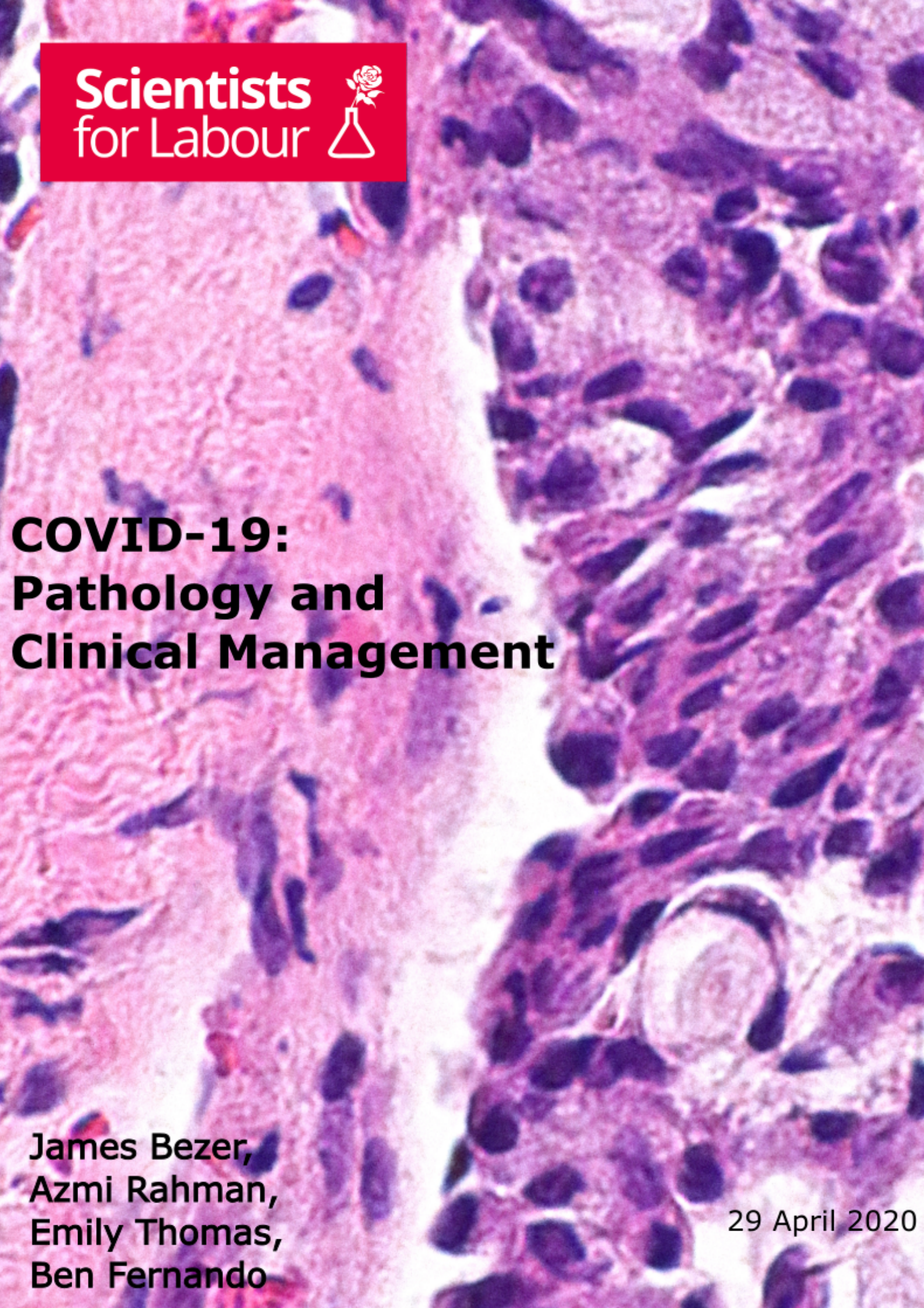

Scientists for Labour

COVID-19: Pathology and Clinical Management

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Scientists for Labour

Scientists for Labour is a socialist society affiliated to the Labour Party. Our aims are to both promote good science in politics, and promote Labour values in science. More information about Scientists for Labour, including how to join, can be found at https://www.scientistsforlabour.org.uk. You can follow us on Twitter @scientists4lab.

Throughout the COVID-19 crisis, Scientists for Labour are preparing briefings and summaries of the latest research into coronavirus for Labour Party representatives and their staff. If you would like to receive these briefings or have any other queries, please contact Benjamin Fernando: chair@sfl.org.uk.

Aims and Scope

This report details the current state of knowledge on pathology and clinical management of COVID-19.

Whilst every effort has been made to validate the statements made in this report we cannot claim that the report is accurate in every regard. Care should be taken when extrapolating from the questions posed here to actual policy, and it should be noted that the situation is changing very rapidly.

Executive Summary

This report summarises the care pathway for COVID-19 in suspected and confirmed cases, based on clinical care guidelines for NHS professionals in the UK.

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. It is a respiratory infection, primarily affecting the throat and lungs. It can be asymptomatic, cause a mild illness affecting the nose and throat, or cause a severe illness affecting the lungs. Most patients are asymptomatic or have a mild illness. Antibiotics will have no benefit in treating the viral infection.

There are no specific treatments for COVID-19 that are currently clinically recommended. Care focuses on symptom management, and supporting organ function in severe cases. Oxygen therapy and ventilation are given for reduced lung function, to ensure patients receive the necessary airflow into their lungs. Continuous Positive Airway Pressure (CPAP), providing pressurised oxygen to the patient via a tightly fitting face mask, is the preferred method of breathing support recommended by NHS England. If this is insufficient, mechanical ventilation (requiring an ICU bed) is offered. Of all patients in the UK admitted to hospital, two thirds received ventilation within 24 hours of admission.

There is a strong global effort to identify new treatments for COVID-19 and emerging treatments are currently being fast tracked through clinical trials.

Contents

1. How Infection Occurs

COVID-19 is disease caused by the virus SARS-CoV-2, a member of a family of viruses known as *Coronaviridae*. This family also includes the viruses that cause SARS, MERS, and the common cold[1].

COVID-19 primarily affects the lungs and respiratory system, but has also been seen to affect the digestive and nervous systems. Many details of the mechanisms by which the virus affects the body remain unknown.

The virus is spread predominantly by droplets from the mouth and nose, due to coughs and sneezes, and also quiet exhalation. There are no reports of airborne transmission (where the virus can spread in the air in the absence of fluid)[2,3]. It is unclear whether transmission may occur through other body fluids.

A small number of studies suggest that some people can be contagious during the incubation period, the time between exposure to the virus and the onset of symptoms. The incubation period is estimated to be around 5 to 7 days, although there is a wide range around this[4]. Of those who develop symptoms, this occurs within 11.5 days of infection in approximately 97.5% of cases[5].

It is believed that many cases may be completely asymptomatic. Estimating how common this is, however, is quite difficult, and studies have produced values as wide ranging as between 4% and 80% of those infected[6].

2. Illness Classification and Symptoms

Those who are infected with the virus can be affected in 4 ways: they may be asymptomatic, have mild illness, develop a lung infection (pneumonia), or develop a severe pneumonia[7].

It is unclear how many patients are asymptomatic (no sign of illness), but it is suspected to be a large proportion of infected individuals[8].

80% of symptomatic patients have a mild illness (fever, fatigue, cough, headache, lack of appetite, tiredness, muscle discomfort, nose congestion). Rarely, patients with mild illness may also have gastrointestinal symptoms such as nausea, vomiting, and diarrhoea. Around 90% of patients have more than one symptom, and 15% have a combination of fever, cough, and shortness of breath[9].

14% of symptomatic patients have severe symptoms, where the infection spreads in the lungs and causes fluid buildup, making it harder to breathe, and harder to clear and treat. 5% of symptomatic patients develop pneumonia that is severe enough to be life threatening[7].

Older people, those with underlying health conditions (such as high blood pressure and diabetes), and those on immunosuppressive medication (transplant patients, HIV) are significantly more likely to develop severe illness. These patients often start with mild symptoms, but have a high risk of deterioration[7,10].

3. How COVID-19 causes Death

The infection most commonly begins in the upper respiratory tract, causing common throat-related symptoms (such as sore throat and cough). If it is does not clear, the infection can travel into the lungs[11].

This lung infection results in inflammation of the lung tissue (a condition called pneumonia). This process causes fluid buildup, preventing the lung from breathing effectively. The greater the fluid buildup, the harder it is to breathe. This causes low oxygen in blood, inducing rapid breathing, bluing skin (cyanosis), confusion – a group of symptoms called acute respiratory distress syndrome (ARDS). If this is not promptly treated with anti-inflammatory medication and supplemental oxygen, this will cause respiratory arrest and death[11].

Patients with COVID-19 can occasionally become severely unwell, with very poor lung function and low oxygen levels, but without any obvious symptoms, or even feeling especially unwell themselves. These individuals can deteriorate very rapidly without warning[10].

The effect of the virus can make the immune system less able to suppress other infections. Secondary bacterial infections are common in seriously ill patients, contributing to illnesses such as bacterial pneumonia or sepsis[7].

4. Clinical Management

There are currently no specific medications approved for COVID-19 infections. Care is focused on relieving symptoms, and supporting organ function in more severe cases.

4.1 Diagnosis and Imaging

The management of a patient suspected to have a COVID-19 infection is strongly dependent on the severity of a patient's symptoms and signs (see *'How the virus causes death'*).

All patients suspected to have COVID-19 will receive a throat swab test, which tests for the presence of COVID-19 viral DNA in the throat. Blood oxygen levels will also be assessed[12].

4.2 Management of Mild Cases

Most cases are mild and can be managed at home during self-isolation, with rest, sufficient hydration, and taking over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs), such as paracetamol or ibuprofen[13]. Some anecdotal reports have suggested that ibuprofen could worsen COVID-19. There is currently no strong evidence to support this[14].

4.3 Management of Cases Requiring Hospital Admission

A patient will be admitted to hospital if they have severe symptoms, or if the patient has less severe illness but suffers from pre-existing conditions or risk factors that make them more likely to deteriorate rapidly. The median time from onset of symptoms to hospital admission is approximately 7 days[13].

<u>Tests done in hospitals</u>

In these patients, blood tests to assess inflammation, and presence of other infections, may be needed.

In all patients where pneumonia (lung infection and inflammation) is suspected, a chest x-ray is performed to look for presence of inflammation and fluid build-up in lungs. This affects one lung in 25% of patients, and both lungs in 75% of patients[15]. In occasional cases where chest X-ray isn't clear, CT or ultrasound imaging is performed.

Whilst in hospital, patient vital signs (heart rate, blood pressure, breathing rate, blood oxygen level) and other infection-related blood levels are monitored.

Treatment of COVID-19

Medical care is provided on a case-by-case basis, based on results of tests and an understanding of the cause of symptoms. In general, the following 2 symptoms/signs are addressed as follows:-

Low Oxygen and Breathlessness: Patients with low blood oxygen levels (<94%) will be given supplemental oxygen[7]. Details of different methods of ventilation are discussed below (see *'Ventilation'*).

Cough: As coughing is a bodily response to clearing the throat, patients are sat up. Medication is offered if cough is severe[13].

Anti-coagulation: New data shows that COVID-19 increases the risk of clotting in adults, which can cause blood clots in the lung that make it hard to breathe, and clots in the brain that cause irreversible damage (stroke)[16]. Anti-coagulants are given to minimise this risk.

How Treatment is offered

In patients with severe symptoms, a clinical frailty score is performed to assess if intensive care is likely to benefit the patient. Patients who are very frail, or who otherwise are not expected to benefit from intensive care, are usually referred instead to end of life care if their condition deteriorates. These decisions are taken in discussion with the patients and their families wherever possible[17].

SARS-CoV-2 and Antibiotics

SARS-CoV-2 is a virus, and antibiotics are ineffective and are not routinely given. Some patients develop secondary bacterial infections, such as bacterial pneumonia or sepsis, which are treated with antibiotics. Because of the risk of antibiotic resistance, and of promoting infections by resistant bacteria such as *C. Difficile*, antibiotics are not recommended as a preventative measure in COVID-19 patients, except in some at high risk of complications[18].

4.4 Intensive Care

Hospital Intensive Care Units (ICU) are reserved for the most severely ill patients, who cannot be cared for sufficiently on a general ward. ICUs provide close monitoring of patients, and advanced life support techniques to keep a person alive when their organs may be failing.

The goal of intensive care medicine is to closely monitor patients and support organ function, to keep patients alive long enough for them to recover from an illness that may otherwise have killed them.

An ICU bed generally includes 1 nurse directly monitoring the patient at all times[19], while less severely ill patients may be treated in high dependency units, which provide a slightly lower intensity of care and staffing levels. Higher staffing is associated with lower mortality in ICU[19].

Intensive care can provide a wide range of care, including mechanical ventilation and kidney dialysis. Cannulas are placed into the large veins in the neck or chest, to provide fluids, medication, or nutrition to a patient who cannot eat. Patients are not necessarily comatose, although they are usually given sedatives to manage pain and if intubated (to prevent choking)[20].

4.5 Ventilation (Oxygen and Breathing Support)

Breathing support is provided to all patients who have difficulty breathing, or have low blood oxygen levels.

The choice of breathing support, and the settings used on each device, such as concentration of oxygen and air pressures used, are tuned to maintain the patient's blood oxygen saturation at a target level. This is measured continuously via an infrared monitor on the finger, and may be periodically measured by arterial blood sampling from the wrist in more seriously ill patients.

NHS England recommends an oxygen saturation target of 92-96%. Excess oxygen saturation (>98%) is abnormal and causes oxygen toxicity[21].

Breathing support can be provided through multiple, increasingly invasive methods. These are listed below[22].

Supplemental Oxygen needed?	Breathing support needed?	Delivery Method
Yes	No	Nasal prongs, face masks
Yes	Mild	CPAP*
Yes	Full	Mechanical Ventilation (Requires Intensive Care)

**CPAP (described below) is recommended by NHS England as the primary mode of breathing support in patients with reduced blood oxygen saturation due to COVID-19.*

Nasal Prongs/Face Masks

Oxygen given via a simple nose tube or facemask. This increases the oxygen going into the lungs, but no pressure is exerted to induce breathing[22].

Continuous Positive Airway Pressure (CPAP)

Patients who find it difficult but are still able to breathe independently may be supported with Continuous Positive Airway Pressure. An airtight mask is placed over either the nose or the whole face, and oxygen is provided at higher than atmospheric pressure. This helps to open up the lungs, making it easier for the patient to breathe[23].

There is some concern that the high pressure oxygen used in CPAP may increase the spread of virus droplets around the patient, especially if the mask is not well sealed. Healthcare providers must therefore take care to protect themselves[17].

In some centres, CPAP has been provided via a plastic helmet or hood, which covers the entire head. This may be more comfortable for patients, whilst providing a better seal, and reducing the risk of droplet spread[24].

Mechanical Ventilation

If a patient becomes unable to breathe well enough on their own, or with non-invasive support, mechanical ventilation may be used. This forces oxygen into the lungs periodically, directly controlling the depth and timing of each breath[22].

Ventilation is most often provided by inserting a tube into their windpipe (tracheal intubation), which is connected to a ventilator. Alternatives such as a laryngeal mask (which sits just above the windpipe) as well[22].

Modern ventilators are complex and have a wide range of settings, which can be optimised to each patient. A ventilator may be used when a patient is able to initiate breaths themselves, where it senses the patient's attempts to breathe, and provides assistance in time with this. In patients with poorer lung function, the ventilator will control the timing and depth of breaths independently[22].

The ventilator provides a higher baseline air pressure than atmospheric pressure, to stop the lungs from becoming totally deflated. This pressure is known as the Positive End-Expiratory Pressure (PEEP). High PEEP may be necessary if breathing is very poor, but is harmful to patients whose lungs are still able to inflate and deflate normally. NHS England recommends a low PEEP in these patients[17,18].

Two-thirds of COVID-19 patients who required critical care in the UK had mechanical ventilation within 24 hours of admission[25]. This is due to the inability to transfer oxygen from the lungs to the blood. Survival rates for patients intubated are around 50%, although this reflects the severity of illness required for a decision to be made to intubate[26].

It is becoming increasingly common to ventilate patients in the prone position, lying on their front. This may improve the transfer of oxygen into the blood, because the parts of the lungs with the best blood supply are less compressed by other organs, such as the liver, enabling better gas exchange[7,17,18,27].

Weaning

Weaning refers to taking a patient of ventilation. This needs to be carefully planned, as a patient who becomes dependent on ventilation will not be able to breathe independently afterward. If patients are expected not to be able to wean off ventilation effectively, that may result in ventilation causing a higher risk than benefit, where ventilation may not be offered to the patient[17].

4.6 Extra-Corporeal Membrane Oxygenation (ECMO)

ECMO is used to provide oxygen to a person whose lungs are not functioning well enough to support them, even with a ventilator. Large cannulas are fed into the heart via the veins or arteries in the neck. These take blood out of the body, where it is saturated with oxygen, before returning it back to the heart. This can ensure the body maintains a good supply of oxygenated blood even in cases of near-total lung failure. This carries risk of clotting, bleeding, infections, and kidney damage, which are avoided unless necessary[17].

While ECMO can prolong life in patients who would otherwise die, it cannot cure those suffering from multiple organ failure. ECMO is therefore only recommended for patients who have a realistic chance of recovery[28]. Preliminary data on the use of ECMO in patients with COVID-19 is not promising, although it may play a useful role in clinical salvaging of select patients[29].

5. Emerging Treatments for COVID-19

With accelerated vaccine programmes unlikely to yield a widely available vaccine in less than 12-18 months managing COVID-19 symptoms at an early stage is vital. Drugs could be given to the already ill or potentially to those at high risk of infection prophylactically[30].

5.1 How are treatments being found?

It is not uncommon for a de novo drug to take at least a decade from initial discovery to approved population wide use. This time includes randomised clinical trials to test the drug which take years alone. Due to the urgent need for treatments for COVID-19, key strategies for accelerating this process include: 1) repurposing existing drugs, 2) considering unapproved drugs which have done well in animal studies against similar coronaviruses and 3) accelerated clinical trials, such as the WHO SOLIDARITY trial which aims to reduce trial time by 80%[30, 31].

5.2 What are the types of potential emerging treatments?

Emerging treatments fall into three categories:

1. Antiviral drugs that directly affect the coronavirus's ability to thrive inside the body
2. Drugs that can calm the immune system - patients become seriously ill when their immune system overreacts and starts causing collateral damage to the body
3. Antibodies, either from survivors' blood or made in a lab, that can attack the virus[32]

Antiviral Drugs: Those available rely on the similarity of SARS-CoV-2 to other viruses. However, as they have been specifically developed for treating a different virus, efficacy against SARS-CoV-2 may differ[33].

Immune System Modulation: This emphasises the importance of understanding the body's response to the virus. The immune response may cause much of the damage to the lungs and targeting the virus without targeting the immune response may not change the patient's prognosis. A combined approach with antivirals may be required. However, dampening the immune system may also increase susceptibility to other infections[34].

Antibodies: Antibodies are defensive proteins produced by the body in response to the virus. This therapy is based on the idea that survivors will have produced neutralising antibodies which are present in their plasma (the liquid component of blood). It is important to note that some antibodies have been associated with a worsening of patient prognosis in response to similar viruses highlighting the importance of understanding the role of antibodies in response to COVID-19[35].

5.3 How treatments are being assessed

Numerous accelerated clinical trials are being conducted globally. 1,509 clinical trials have been registered and 145 drugs identified as potential candidates as of 22/04/2020[31]. In an attempt to coordinate the international clinical trial landscape, the WHO has launched the SOLIDARITY master protocol establishing consistent end points, control arms and inclusion–exclusion criteria. This aims to increase the value of the emerging trial data set[36].

This umbrella trial, SOLIDARITY, is being conducted by the WHO to test four potential treatments:

1. **Remdesivir:** Antiviral previously tested as an Ebola treatment. It has promising results in animal studies for similar coronaviruses - Middle East Respiratory Syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS).
2. **Chloroquine or Hydroxychloroquine:** Used to treat malaria. In China and France, small studies provided some indications of possible benefit of chloroquine against pneumonia caused by COVID-19 but need confirmation through randomized trials.

3. **Lopinavir with Ritonavir:** Licensed treatment for HIV. While there are indications from laboratory experiments that this combination may be effective against COVID-19, studies done so far in COVID-19 patients have been inconclusive.
4. **Lopinavir with Ritonavir plus Interferon beta-1a:** Inteferon beta-1a belongs to a class of molecules among the first to be produced by the body against viruses[31, 37].

Countries have the option of adding other treatment arms to their trial as necessary[31]. The first results could be expected in 12-16 weeks (estimated late Summer onwards)[38].

Another large trial is based in the UK, RECOVERY (in hospital trial). RECOVERY is led by a team at the University of Oxford and has over 5000 participants. The study has received £2.1 million from UK Research and Innovation (UKRI) and the Department of Health and Social Care, through the National Institute of Health Research (NIHR). This is part of the £20 million rapid research response investment by the government to support looking at ways to tackle the coronavirus outbreak[39].

Two other key UK trials are PRINCIPLE (higher risk patients in primary care trial) and REMAP-CAP (critically ill patient trial)[40].

A nationwide trial investigating plasma treatment, with more than 600 participants, is currently underway in the US[41]. The NHS Blood and Transplant Centre is currently reaching out to COVID-19 survivors for a similar trial in the UK[42].

5.4 What can the UK government do to help develop treatments?

1. Can the government expand on what efforts it is undertaking to support therapeutic research and clinical trials?
2. Has the government expanded the collection of statistics at every stage of the treatment process, to ensure that efficacy can be better evaluated in both close-to-real-time, and in subsequent analyses; especially for non-pharmaceutical treatments?
3. Can the government expand on how they aim to reduce legislative hurdles to accelerate clinical trials and grant approval for new emergency therapeutics?
4. Many of the most promising drugs currently in clinical trials are estimated to be cheap to manufacture. One day's supply of remdesivir is estimated to cost $0.93 to manufacture. Following the call led by Doctors without Borders, can the government expand on their plans to ensure that limited supply and patent protection do not inhibit the affordability of potential emerging treatments?[43]
5. Can the government expand on their plans to ensure that should a promising foreign-developed treatment be found to be effective for COVID-19, the UK will have access to the drug?[44]
6. Given that no pharmaceutical products have yet been shown to be safe and effective for the treatment of COVID-19 but many may be promising. And, given the need to preserve stocks of these drugs to treat the illnesses for which they are designed and be maintained for use in clinical trials. Can the government expand on their plans for allowing compassionate use?

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