

COVID-19 rapid guideline: Managing COVID-19

Main editor

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Contact

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Summary of recommendations

1. How to use this guideline

2. Introduction

3. Definition of disease severity

4. Communication and shared decision making

Consensus recommendation

Communicate with people with COVID-19, and their families and carers, and support their mental wellbeing to help alleviate any anxiety and fear they may have. Signpost to charities and support groups (including NHS Volunteer Responders), to [NHS every mind matters](#) and to [Royal College of Paediatrics and Child Health resources for parents and carers](#).

Remark: Give people information in a way that they can use and understand, to help them take part in decisions about their care. Follow relevant national guidance on communication, providing information (including in different formats and languages) and shared decision making, for example, [NICE's guideline on patient experience in adult NHS services](#).

The [Royal College of Obstetricians and Gynaecologists](#) has produced information on COVID-19 and pregnancy for pregnant women and their families.

Consensus recommendation

For adults with COVID-19, explain:

- that the typical symptoms are cough, fever, and loss of sense of smell or taste, but that they may also have breathlessness (which may cause anxiety), delirium (which may cause agitation), fatigue, headache, muscle aches and sore throat
- that other symptoms may be drowsiness (particularly in older people), poor appetite, and chest discomfort or pain
- that they and people in close contact with them or in the same household (including those caring for them) should follow [Public Health England's stay at home: guidance for households with possible or confirmed coronavirus \(COVID-19\) infection](#) and the [UK government guidance on protecting vulnerable people](#)
- that they are likely to feel much better in a week if their symptoms are mild
- who to contact if their symptoms get worse, for example, [NHS 111 online](#).

Consensus recommendation

For carers of people with COVID-19 who should isolate but are unable to (for example, people with dementia), signpost to relevant support and resources.

Remark: For example, the [Alzheimer's Society](#) has information on staying safe from coronavirus and reducing the risk of infection.

Consensus recommendation

For children and young people under 18 years with COVID-19, explain:

- that additional symptoms (to those found in adults) may include grunting, nasal flare, nasal congestion, poor appetite, gastrointestinal symptoms, skin rash and conjunctivitis
- that they and people in close contact with them or in the same household (including those caring for them) should follow [Public Health England's stay at home: guidance for households with possible or confirmed coronavirus \(COVID-19\) infection](#)
- that they are likely to feel much better in a week if their symptoms are mild
- who to contact if their symptoms get worse, for example, [NHS 111 online](#)
- that the presence of fever, rash, abdominal pain, diarrhoea or vomiting may indicate paediatric inflammatory multisystem syndrome (PIMS)
- how and when to seek medical help if PIMS is suspected.

Consensus recommendation

In the community, consider the risks and benefits of face-to-face and remote care for each person. Where the risks of face-to-face care outweigh the benefits, remote care can be optimised by:

- offering telephone or video consultations (see [BMJ guidance on Covid-19: a remote assessment in primary care](#) for a useful guide, including a [visual summary for remote consultation](#))
- cutting non-essential face-to-face follow up
- using electronic prescriptions rather than paper
- using different methods to deliver medicines to people, for example, pharmacy deliveries, postal services and NHS volunteers, or introducing drive-through pick-up points for medicines.

Consensus recommendation

When possible, discuss the risks, benefits and possible likely outcomes of the treatment options with people with COVID-19, and their families and carers. Use decision support tools (when available).

Remark: This will help people express their preferences about their treatment and escalation plans. Bear in mind that these discussions may need to take place remotely.

Consensus recommendation

For people with pre-existing advanced comorbidities, find out if they have advance care plans or advance decisions to refuse treatment, including do not attempt cardiopulmonary resuscitation decisions. Document this clearly and take account of these in planning care.

5. Assessment

5.1 In the community

Consensus recommendation

5.1.1 Identifying severe COVID-19 Use the following signs and symptoms to help identify people with COVID-19 with the most severe illness:

- severe shortness of breath at rest or difficulty breathing
- reduced oxygen saturation levels measured by pulse oximetry (see the [recommendation on pulse oximetry levels that indicate serious illness](#))
- coughing up blood
- blue lips or face
- feeling cold and clammy with pale or mottled skin
- collapse or fainting (syncope)
- new confusion
- becoming difficult to rouse
- reduced urine output.

Remark: For signs and symptoms to help identify paediatric inflammatory multisystem syndrome (PIMS) temporarily associated with COVID-19, see the [guidance on PIMS from the Royal College of Paediatrics and Child Health](#).

Consensus recommendation

When pulse oximetry is available in primary and community care settings, to assess the severity of illness and detect early deterioration, use:

- [NHS England's guide to pulse oximetry](#) in people 18 years and over with COVID-19
- oxygen saturation levels below 91% in room air at rest in children and young people (17 years and under) with COVID-19.

Remark: Be aware that different pulse oximeters have different specifications, and that some can under- or overestimate readings especially if the saturation level is borderline. Overestimation has been reported in people with dark skin.

Info Box

Assessing shortness of breath (dyspnoea) is important, but may be difficult via remote consultation. Tools such as the [Medical Research Council's dyspnoea scale](#) or the [Centre for Evidence Based Medicine's review of ways of assessing dyspnoea \(breathlessness\) by telephone or video](#) can be useful.

The [NEWS2 tool](#) may be used in adults in addition to clinical judgment to assess a person's risk of deterioration. Note that use of [NEWS2](#) is not advised in children or pregnant women. Although the [NEWS2 tool](#) is not validated for predicting the risk of clinical deterioration in prehospital settings, it may be a helpful adjunct to clinical judgement in adults. A face-to-face consultation should not be arranged solely to calculate a [NEWS2](#) score.

Locally approved Paediatric Early Warning Scores should be used for children. When using early warning scores, ensure that readings are based on calibrated machines. Be aware that readings may be incomplete when doing remote consultations.

Consensus recommendation

For people with severe respiratory symptoms associated with COVID-19 (for example, suspected pneumonia) being managed in the community, see the [recommendation on venous thromboembolism in hospital-led acute care in the community](#).

Consensus recommendation

5.1.2 Care planning Discuss with people with COVID-19, and their families and carers, the benefits and risks of hospital admission or other acute care delivery services (for example, virtual wards or hospital at home teams).

Remark: Some benefits and risks may be similar for all patients (for example, improved diagnostic tests and access to treatments, or better contact with families in the community), but others may be personal to the individual (such as loss of access to carers who can anticipate needs well in someone unable to communicate themselves, or risks of spreading COVID-19).

Consensus recommendation

Explain that people with COVID-19 may deteriorate rapidly. Discuss future care preferences at the first assessment to give people who do not have existing advance care plans an opportunity to express their preferences.

5.2 In hospital

Consensus recommendation

When a person is admitted to hospital with COVID-19, ensure a holistic assessment is done, including discussion about their treatment expectations and care goals:

- Document and assess the stability of underlying health conditions, involving relevant specialists as needed.
- Use the Clinical Frailty Scale (CFS) when appropriate, available from the NHS Specialised Clinical Frailty Network, to assess baseline health and inform discussions on treatment expectations.
- Use the CFS within an individualised assessment of frailty.
- Do not use the CFS for younger people, people with stable long-term disabilities (for example, cerebral palsy), learning disabilities or autism. Make an individualised assessment of frailty in these people, using clinical assessment and alternative scoring methods.
- Record the assessment and discussion in the person's medical records.

Remark: For assessment of paediatric inflammatory multisystem syndrome (PIMS), follow the [guidance on PIMS from the Royal College of Paediatrics and Child Health](#).

Consensus recommendation

When making decisions about the care of children and young people under 18 years, people with learning disabilities or adults who lack mental capacity for health decision making, for example, people with advanced dementia, see the [NICE guideline on decision-making and mental capacity](#).

Ensure discussions on significant care interventions involve families and carers as appropriate, and local experts or advocates.

6. Management

6.1 In the community

6.1.1 Care planning

Consensus recommendation

Put treatment escalation plans in place in the community after sensitively discussing treatment expectations and care goals with people with COVID-19, and their families and carers.

Remark: People with COVID-19 may deteriorate rapidly. If it is agreed that the next step is a move to secondary care, ensure that they and their families understand how to access this with the urgency needed. If the next step is other community-based support (whether virtual wards, hospital at home services or palliative care), ensure that they and their families understand how to access these services, both in and out of hours.

6.1.2 Managing cough

Consensus recommendation

Encourage people with cough to avoid lying on their backs, if possible, because this may make coughing less effective.

Remark: Be aware that older people or those with comorbidities, frailty, impaired immunity or a reduced ability to cough and clear secretions are more likely to develop severe pneumonia. This could lead to respiratory failure and death.

Consensus recommendation

Use simple measures first, including advising people over 1 year with cough to take honey.

Remark: The dose is 1 teaspoon of honey.

Consensus recommendation

Consider short-term use of codeine linctus, codeine phosphate tablets or morphine sulfate oral solution in people 18 years and over to suppress coughing if it is distressing. Seek specialist advice for people under 18 years.

Remark: See practical info for dosages for treatments to manage cough in people 18 years and over.

6.1.3 Managing fever

Consensus recommendation

Advise people with COVID-19 and fever to drink fluids regularly to avoid dehydration. Support their families and carers to help when appropriate. Communicate that fluid intake needs can be higher than usual because of fever.

Consensus recommendation

Advise people to take paracetamol or ibuprofen if they have fever and other symptoms that antipyretics would help treat. Tell them to continue only while both the symptoms of fever and the other symptoms are present.

Remark: People can take paracetamol or ibuprofen when self-medicating for symptoms of COVID-19, such as fever (see the [Central Alerting System: novel coronavirus - anti-inflammatory medications](#) for further details of ibuprofen including dosage).

For people 18 years and over, the paracetamol dosage is 1 g orally every 4 to 6 hours (maximum 4 g per day). See the [BNF](#) and [Medicines and Healthcare products Regulatory Agency advice](#) for appropriate use and dosage in specific adult populations.

For children and young people over 1 month and under 18 years, see the dosing information on the pack or the [BNF for children](#).

Rectal paracetamol, if available, can be used as an alternative. For rectal dosage information, see the BNF and BNF for children.

6.1.4 Managing breathlessness

Consensus recommendation

Identify and treat reversible causes of breathlessness, for example, pulmonary oedema, pulmonary embolism, chronic obstructive pulmonary disorder and asthma.

Remark: For further information on identifying and managing pulmonary embolism, see the [NICE guideline on venous thromboembolic diseases: diagnosis, management and thrombophilia testing](#).

Consensus recommendation

When significant medical pathology has been excluded or further investigation is inappropriate, the following may help to manage breathlessness as part of supportive care:

- keeping the room cool
- encouraging relaxation and breathing techniques, and changing body positioning
- encouraging people who are self-isolating alone to improve air circulation by opening a window or door.

If hypoxia is the likely cause of breathlessness:

- consider a trial of oxygen therapy
- discuss with the person, their family or carer possible transfer to and evaluation in secondary care.

Remark: Breathlessness with or without hypoxia often causes anxiety, which can then increase breathlessness further.

6.1.5 Managing anxiety, delirium and agitation

Consensus recommendation

Assess reversible causes of delirium. See the [NICE guidance on delirium: prevention, diagnosis and management](#).

Consensus recommendation

Address reversible causes of anxiety by:

- exploring the person's concerns and anxieties
- explaining to people providing care how they can help.

Consensus recommendation

Consider trying a benzodiazepine to manage anxiety or agitation. See practical info for treatments for managing anxiety, delirium and agitation in people 18 years and over. Seek specialist advice for people under 18 years.

6.1.6 Managing medicines

Consensus recommendation

When supporting people with symptoms of COVID-19 who are having care in the community delivered by social care, follow the [NICE guideline on managing medicines for adults receiving social care in the community](#). This includes processes for ordering and supplying medicines, and transporting, storing and disposing of medicines.

Consensus recommendation

When prescribing, handling, administering and disposing of medicines in care homes and hospices follow the [NICE guideline on managing medicines in care homes](#) and the [UK government COVID-19 standard operating procedure for running a medicines re-use scheme in a care home or hospice setting](#).

6.2 In hospital

6.2.1 Deciding when to escalate treatment

Consensus recommendation

Base decisions about escalating treatment within the hospital on the likelihood of a person's recovery. Take into account their treatment expectations, goals of care and the likelihood that they will recover to an outcome that is acceptable to them.

Remark:

For support with decision making, see:

- [advice on ethics from the British Medical Association](#)
- [ethical guidance from the Royal College of Physicians](#)
- [national guidance presented by the Faculty of Intensive Care Medicine, Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists](#)
- [advice on decision making under pandemic conditions by the Intensive Care Society](#), and
- [advice on decision making and consent from the General Medical Council](#)

Consensus recommendation

Ensure healthcare professionals have access to resources to support discussions about treatment plans (see, for example, [decision-making for escalation of treatment and referring for critical care support](#), and an example [decision support form](#)).

Remark:

Tools such as the [British Medical Journal emergency care and resuscitation plan](#) may be useful when making decisions about a treatment plan.

Consensus recommendation

Discuss treatment escalation with a multidisciplinary team of medical and allied health professional colleagues (such as from critical care, respiratory medicine, geriatric medicine and palliative care) when there is uncertainty about treatment escalation decisions.

Consensus recommendation

Document referral to and advice from critical care services and respiratory support units in a standard format. When telephone advice from critical care or respiratory support units is appropriate, this should still be documented in a standard format (see [an example of a tool for documentation](#)).

6.2.2 Escalating and de-escalating treatment

Consensus recommendation

Before escalating respiratory or other organ support, identify agreed treatment goals with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate). Start all advanced respiratory support or organ support with a clear plan of how it will address the diagnosis and lead to agreed treatment goals (outcomes). Ensure this includes management plans for when there is further deterioration or no response to treatment.

Do not continue respiratory or other organ support if it is considered that it will no longer result in the desired overall goals (outcomes). Record the decision and the discussion with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate).

6.2.3 Delivering services in critical care and respiratory support units

Consensus recommendation

Trusts should review:

- their strategy on management for people who are deteriorating and
- use of the track-and-trigger system (NEWS2 has been endorsed by NHS England and Improvement).

See the [NICE guideline on acutely ill adults in hospital for recommendations on identifying patients whose clinical condition is deteriorating or is at risk of deterioration](#).

Remark: See the [Royal College of Physician's information on the place of NEWS2 in managing patients with COVID-19](#).

6.2.4 Non-invasive respiratory support

Info Box

Definitions

High-flow nasal oxygen (HFNO): involves the delivery of warm and humidified oxygen (up to 60 litres per minute) through a small nasal cannula. The delivered flow is higher than the flow of air when the person is breathing in (inspiratory flow). HFNO can also deliver a higher concentration of oxygen than supplemental oxygen alone.

Continuous positive airway pressure (CPAP): is a type of positive airway pressure that delivers a set pressure of airflow to the airways. This pressure is maintained throughout the respiratory cycle, both when the person is breathing in (inspiration) and breathing out (expiration). A CPAP device consists of a unit that generates airflow, which is delivered to the airway through a tight-fitting mask or other airtight interface.

Non-invasive ventilation (NIV): refers to a mode of positive pressure ventilation that delivers airflow to the airways through a tight-fitting mask or other airtight interface. Airflow is delivered at variable pressures that are higher than when the person is breathing in (inspiratory pressure) and lower than when the person is breathing out (expiratory pressure).

Non-invasive respiratory support: is a broad umbrella term for different types of non-invasive respiratory support, such as HFNO, CPAP and NIV. They are considered to be a more intensive intervention than oxygen therapy alone. The different types of support are not, however, interchangeable with each other because they have differing effects on a person's physiology. So, they typically have different indications for their use.

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the [Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'](#).

Info Box

For information on deciding when to escalate and de-escalate treatment, see the [sections on deciding when to escalate treatment](#) and [escalating and de-escalating treatment](#). Also, consider factors such as:

- how much supplemental oxygen is needed to reach target oxygen saturation
- the overall clinical trajectory
- assessment of work of breathing
- how well treatment will be tolerated
- treatment preferences after discussion with the person, and their family and carers when appropriate.

Remark:

The [Royal College of Obstetricians and Gynaecologists](#) has produced information on management of coronavirus infection in pregnancy.

Info Box

For information on how to manage COVID-19 in people who are having non-invasive respiratory support, see the [sections on management](#) and [therapeutics for COVID-19](#).

Consensus recommendation

Ensure that pharmacological and non-pharmacological management strategies, including body positioning, are optimised before escalating treatment to non-invasive respiratory support.

Remark:

The [Royal College of Obstetricians and Gynaecologists](#) has produced information on management of coronavirus infection in pregnancy.

Conditional recommendation against

Do not routinely offer high-flow nasal oxygen as the main form of respiratory support for people with COVID-19 and respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate.

Conditional recommendation

Consider offering continuous positive airway pressure (CPAP) to people with COVID-19 when:

- they have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 0.4 (40%) or more, **and**
- escalation to invasive mechanical ventilation would be an option but it is not immediately needed, **or**
- it is agreed that respiratory support should not be escalated beyond CPAP.

Remark:

In June 2021, the [Medicines and Healthcare products Regulatory Agency](#) issued a [National Patient Safety Alert for Philips ventilator, CPAP and bilevel positive airway pressure devices](#) because of a potential for harm from inhaled particles and volatile organic compounds. This applies to all devices manufactured before 26 April 2021.

For information on decision making and giving advice, see the [British Thoracic Society risk stratification guidance on Philips ventilator, CPAP and bilevel positive airway pressure devices](#).

Consensus recommendation

For people with COVID-19 having continuous positive airway pressure, ensure:

- there is access to critical care providers for advice, review and prompt escalation of treatment if needed (such as when treatment has failed)
- regular review by an appropriate senior clinician (such as every 12 hours) and more frequent review if needed, in line with the British Thoracic Society guidance on respiratory support units and the Faculty of Intensive Care Medicine guidelines on the provision of intensive care services
- regular assessment and management of symptoms alongside non-invasive respiratory support.

Remark:

Staff caring for people with COVID-19 having CPAP should have appropriate skills and competencies and provide appropriate monitoring. For further information on standards of care and provision of services see the [Faculty of Intensive Care Medicine and Intensive Care Society guidelines on the provision of intensive care services](#) and the [British Thoracic Society and Intensive Care Society guidance on development and implementation of respiratory support units](#).

Consensus recommendation

Consider using high-flow nasal oxygen for people having continuous positive airway pressure (CPAP) when they need:

- a break from CPAP, such as at mealtimes
- humidified oxygen
- weaning from CPAP.

7. Therapeutics for COVID-19

7.1 Corticosteroids

Recommended

Offer dexamethasone, or either hydrocortisone or prednisolone when dexamethasone cannot be used or is unavailable, to people with COVID-19 who:

- need supplemental oxygen to meet their prescribed oxygen saturation levels or
- have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it.

Continue corticosteroids for up to 10 days unless there is a clear indication to stop early, which includes discharge from hospital or a hospital-supervised virtual COVID ward.

Remark: Being on a hospital-supervised virtual COVID ward is not classed as being discharged from hospital.

See Practical info for dosage information.

For full details of adverse events and contraindications, see the summaries of product characteristics.

For children with a greater than 44-week corrected gestational age, follow the [risk criteria set out in Royal College of Paediatric and Child Health guidance for assessing children admitted to hospital with COVID-19](#). For preterm babies with a corrected gestational age of less than 44 weeks, seek specialist advice.

Conditional recommendation against

Do not routinely use corticosteroids to treat COVID-19 in people who do not need supplemental oxygen, unless there is another medical indication to do so.

7.2 Casirivimab and imdevimab - for people hospitalised because of COVID-19

Recommended Updated

Offer a combination of casirivimab and imdevimab to people aged 12 and over hospitalised because of COVID-19 who have no detectable SARS-CoV-2 antibodies (seronegative).

Remark:

The criteria for accessing casirivimab and imdevimab in the UK, and dosage to be used, are outlined in [NHS England's Interim Clinical Commissioning Policy on casirivimab and imdevimab for patients hospitalised due to COVID-19 \(aged 12 years and above\)](#), published in September 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given casirivimab and imdevimab.

Not recommended Updated

Do not offer a combination of casirivimab and imdevimab to people aged 12 and over hospitalised because of COVID-19:

- who have detectable SARS-CoV-2 antibodies (seropositive), or
- whose serostatus is unknown.

7.3 Remdesivir

Info Box

Definitions

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the [Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'](#).

Low-flow oxygen supplementation: oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min.

Conditional recommendation

Consider remdesivir for up to 5 days for COVID-19 pneumonia in adults, and young people 12 years and over weighing 40 kg or more, in hospital and needing low-flow supplemental oxygen.

Remark:

The criteria for accessing remdesivir in the UK are outlined in [NHS England's Interim Clinical Commissioning Policy on remdesivir for patients hospitalised with COVID-19 \(adults and children 12 years and older\)](#), which was updated in June 2021 to include eligibility criteria for remdesivir in people who are significantly immunocompromised.

For remdesivir use in pregnancy, follow the [Royal College of Obstetrics and Gynaecology guidance on coronavirus \(COVID-19\) infection and pregnancy](#).

The marketing authorisation for remdesivir for COVID-19 does not include children under 12 years or weighing less than 40 kg.

Only in research settings

Do not use remdesivir for COVID-19 pneumonia in adults, young people and children in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive mechanical ventilation or invasive mechanical ventilation, except as part of a clinical trial.

7.4 Tocilizumab

Info Box

Definition

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the [Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'](#).

Recommended

Updated

Offer tocilizumab to adults in hospital with COVID-19 if all the following apply:

- they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
- they have not had another interleukin-6 inhibitor during this admission
- there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab.

And they:

- need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
- are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

Remark:

In October 2021, the marketing authorisations for tocilizumab do not cover use in COVID-19. See [NICE's information on prescribing medicines for more about off-label and unlicensed use of medicines](#).

The recommended dosage for tocilizumab is a single dose of 8 mg/kg by intravenous infusion. The total dose should not exceed 800 mg.

For tocilizumab use in pregnancy, follow the [Royal College of Obstetrics and Gynaecology guidance on coronavirus \(COVID-19\) infection and pregnancy](#).

For full details of adverse events and contraindications, see the summaries of product characteristics for tocilizumab.

See [NHS England's Interim Clinical Commissioning Policy on tocilizumab for hospitalised patients with COVID-19 pneumonia \(adults\)](#) for further information.

Only in research settings

Consider tocilizumab for children and young people who have severe COVID-19 or paediatric inflammatory multisystem syndrome only if they are 1 year and over, and only in the context of a clinical trial.

7.5 Sarilumab

Info Box

Definition

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the [Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'](#).

Conditional recommendation

Updated

Consider sarilumab for COVID-19 in adults in hospital if tocilizumab is unavailable for this condition or cannot be used. Use the same eligibility criteria as those for tocilizumab. That is, if all the following apply:

- they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
- they have not had another interleukin-6 inhibitor during this admission
- there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by sarilumab.

And they:

- need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
- are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

Remark:

In October 2021, the marketing authorisations for sarilumab do not cover use in COVID-19. See [NICE's information on prescribing medicines for more about off-label and unlicensed use of medicines](#).

The recommended dosage for sarilumab is a single dose of 400 mg by intravenous infusion.

For sarilumab use in pregnancy, follow the [Royal College of Obstetrics and Gynaecology guidance on coronavirus \(COVID-19\) infection and pregnancy](#).

For full details of adverse events and contraindications, see the summaries of product characteristics.

See [NHS England's Interim Clinical Commissioning Policy on sarilumab for critically ill patients with COVID-19 pneumonia \(adults\)](#) for further information.

7.6 Low molecular weight heparins

Info Box

For recommendations on the therapeutic use of low molecular weight heparins, see the [section on venous thromboembolism \(VTE\) prophylaxis](#).

7.7 Vitamin D supplementation

Info Box

For recommendations on vitamin D, see the [NICE COVID-19 rapid guideline on vitamin D](#).

7.8 Antibiotics

Info Box

Antibiotics should not be used for preventing or treating COVID-19 unless there is clinical suspicion of additional bacterial co-infection. See the [section on suspected or confirmed co-infection](#).

See also the recommendations on [azithromycin](#) and [doxycycline](#) in the section on therapeutics for COVID-19.

7.9 Azithromycin



Not recommended

Do not use azithromycin to treat COVID-19.

7.10 Budesonide (inhaled)



Only in research settings

New

Only use budesonide to treat COVID-19 as part of a clinical trial.

Remark:

People already on budesonide for conditions other than COVID-19 should continue treatment if they test positive for COVID-19.

7.11 Colchicine



Not recommended

Do not offer colchicine to people in hospital to treat COVID-19.

Remark: NICE is aware that there is newly published evidence on colchicine from the RECOVERY trial and this is being reviewed.



Only in research settings

Only use colchicine to treat COVID-19 in community settings as part of a clinical trial.

7.12 Doxycycline



Not recommended

Do not use doxycycline to treat COVID-19 in the community.

7.13 Ivermectin



Only in research settings

New

Do not use ivermectin to treat COVID-19 except as part of a clinical trial.

7.14 Ongoing review of therapeutics for COVID-19



Info Box

We are currently reviewing new and existing therapeutics for treating COVID-19 as part of a living guidelines approach. New and updated recommendations will be published for this guideline as they become available (see [Update information](#) | [COVID-19 rapid guideline: managing COVID-19](#) | [Guidance](#) | NICE).

8. Preventing and managing acute complications

8.1 Acute kidney injury (AKI)

Info Box

In people with COVID-19, AKI:

- may be common, but prevalence is uncertain and depends on clinical setting (the [Intensive Care National Audit and Research Centre's report on COVID-19 in critical care](#) provides information on people in critical care who need renal replacement therapy for AKI)
- is associated with an increased risk of dying
- can develop at any time (before, during or after hospital admission)
- may be caused by volume depletion (hypovolaemia), haemodynamic changes, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology or rhabdomyolysis
- may be associated with haematuria, proteinuria and abnormal serum electrolyte levels (both increased and decreased serum sodium and potassium).

Info Box

In people with COVID-19:

- maintaining optimal fluid status (euvolaemia) is difficult but critical to reducing the incidence of AKI
- treatments for COVID-19 may increase the risk of AKI
- treatments for pre-existing conditions may increase the risk of AKI
- fever and increased respiratory rate increase insensible fluid loss.

8.1.1 Assessing and managing acute kidney injury (AKI)

Info Box

The potassium binders patiomer and sodium zirconium cyclosilicate can be used as options alongside standard care for the emergency management of acute life-threatening hyperkalaemia (see [NICE's technology appraisal guidance on patiomer](#) and [sodium zirconium cyclosilicate](#) for treating hyperkalaemia).

Info Box

For information on assessing and managing AKI, see the [NICE guideline on acute kidney injury: prevention, detection and management](#).

For information on using intravenous fluids, see the [NICE guideline on intravenous fluid therapy in adults in hospital](#) and the [NICE guideline on intravenous fluid therapy in children and young people in hospital](#).

For information on managing renal replacement therapy for adults who are critically unwell with COVID-19, see the [Renal Association's guidelines on renal replacement therapy for critically unwell adults](#).

8.1.2 Follow up

Consensus recommendation

Monitor people with chronic kidney disease for at least 2 years after AKI, in line with the [NICE guideline on chronic kidney disease: assessment and management](#).

Remark: See guidance on care after hospital discharge in the [Royal College of General Practitioners AKI toolkit](#).

8.2 Acute myocardial injury

8.2.1 Diagnosing acute myocardial injury

Consensus recommendation

For people in hospital with COVID-19 with signs or symptoms that suggest acute myocardial injury, measure high sensitivity troponin I (hs-cTnI) or T (hs-cTnT) and N-terminal pro B-type natriuretic peptide, and do an ECG.

Use the following test results to help inform a diagnosis:

- evolving ECG changes suggesting myocardial ischaemia
- an NT-proBNP level above 400 ng/litre
- high levels of hs-cTnI or hs-cTnT, particularly levels increasing over time.

Info Box

Elevated troponin levels may reflect cardiac inflammatory response to severe COVID-19 rather than acute coronary syndrome.

8.2.2 Managing myocardial injury

Consensus recommendation

For all people with COVID-19 and suspected or confirmed acute myocardial injury:

- monitor in a setting where cardiac or respiratory deterioration can be rapidly identified
- do continuous ECG monitoring
- monitor blood pressure, heart rate and fluid balance.

Consensus recommendation

For people with a clear diagnosis of myocardial injury:

- seek specialist cardiology advice on treatment, further tests and imaging
- follow local treatment protocols.

Consensus recommendation

For people with a high clinical suspicion of myocardial injury, but without a clear diagnosis:

- repeat high sensitivity troponin (hs-cTnI or hs-cTnT) measurements and ECG monitoring daily, because dynamic change may help to monitor the course of the illness and establish a clear diagnosis
- seek specialist cardiology advice on further investigations such as transthoracic echocardiography and their frequency.

Remark: See also the management section for [recommendations on care planning](#) and [recommendations on escalating and de-escalating treatment](#).

Info Box

See the [Medicines and Healthcare products Regulatory Agency's Drug Safety Update on erythromycin: caution required due to cardiac risks \(QT interval prolongation\)](#); drug interaction with rivaroxaban.

8.3 Venous thromboembolism (VTE) prophylaxis



Info Box

Definitions

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the [Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'](#).

Hospital-led acute care in the community: a setting in which people who would otherwise be admitted to hospital have acute medical care provided by members of the hospital team, often working with the person's GP team. They include hospital at home services and COVID-19 virtual wards.

Standard prophylactic dose: the prophylactic dose of a low molecular weight heparin (LMWH), as listed in the medicine's summary of product characteristics, for medical patients.

Intermediate dose: double the standard prophylactic dose of an LMWH for medical patients.

A treatment dose: the licensed dose of anticoagulation used to treat confirmed VTE.

8.3.1 In hospital



Consensus recommendation

For young people and adults with COVID-19 that is being managed in hospital, assess the risk of bleeding as soon as possible after admission or by the time of the first consultant review. Use a risk assessment tool published by a national UK body, professional network or peer-reviewed journal.

Remark:

The [Department of Health VTE risk assessment tool](#) is commonly used to develop treatment plans.



Recommended

Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and who do not have an increased bleeding risk.

Treatment should be continued for a minimum of 7 days, including after discharge.

See the [NICE recommendation on low molecular weight heparin self-administration](#).

Conditional recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk.

Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances.

Remark:

For people with COVID-19 who do not need low-flow oxygen, follow the [recommendations in NICE's guideline on venous thromboembolism in over 16s](#).

In August 2021, using a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. See [NICE's information on prescribing medicines](#).

Only in research settings

Only offer an intermediate or treatment dose of a low molecular weight heparin to young people and adults with COVID-19 who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation as part of a clinical trial.

Consensus recommendation

Do not base prophylactic dosing of heparin on levels of D-dimer.

Consensus recommendation

For people at extremes of body weight or with impaired renal function, consider adjusting the dose of low molecular weight heparins in line with the summary of product characteristics and locally agreed protocols.

Consensus recommendation

For people who cannot have low molecular weight heparins (LMWHs), use fondaparinux sodium or unfractionated heparin (UFH).

Remark:

In August 2021, LMWHs and fondaparinux sodium were off label for people under 18 years. See [NICE's information on prescribing medicines](#).

Consensus recommendation

For people who are already having anticoagulation treatment for another condition when admitted to hospital:

- continue their current treatment dose of anticoagulant unless contraindicated by a change in clinical circumstances
- consider switching to a low molecular weight heparin (LMWH) if their current anticoagulant is not an LMWH and their clinical condition is deteriorating.

Consensus recommendation

If a person's clinical condition changes, assess the risk of VTE, reassess bleeding risk and review VTE prophylaxis.

Consensus recommendation

Organisations should collect and regularly review information on bleeding and other adverse events in people with COVID-19 having treatment or intermediate doses of low molecular weight heparins.

Consensus recommendation

Ensure that people who will be completing VTE prophylaxis after discharge from hospital are able to use it correctly or have arrangements made for someone to help them.

8.3.1.1 In hospital-led acute care in the community

Consensus recommendation

For people with COVID-19 managed in hospital-led acute care in the community settings:

- assess the risks of VTE and bleeding
- consider pharmacological prophylaxis if the risk of VTE outweighs the risk of bleeding.

8.3.2 People with COVID-19 and additional risk factors

Consensus recommendation

For women with COVID-19 who are pregnant or have given birth within the past 6 weeks, follow the [advice on VTE prevention in the Royal College of Obstetricians and Gynaecologists guidance on coronavirus \(COVID-19\) in pregnancy](#).

Consensus recommendation

For children with COVID-19 admitted into hospital, follow the advice on [COVID-19 guidance for management of children admitted to hospital in the Royal College of Paediatrics and Child Health guidance](#).

8.3.3 Information and support

Consensus recommendation

Give people with COVID-19, and their families or carers if appropriate, information about the benefits and risks of VTE prophylaxis.

Remark: See the [recommendations on giving information and planning for discharge in the NICE guideline on venous thromboembolism in over 16s](#), including information on alternatives to heparin for people who have concerns about using animal products.

Consensus recommendation

Offer people the opportunity to take part in ongoing clinical trials on COVID-19.

8.4 Suspected or confirmed co-infection

Consensus recommendation

Do not offer an antibiotic for preventing or treating pneumonia if SARS-CoV-2, another virus, or a fungal infection is likely to be the cause.

Remark: Antibiotics do not work on viruses, and inappropriate antibiotic use may reduce availability. Also, inappropriate use may lead to *Clostridioides difficile* infection and antimicrobial resistance, particularly with broad-spectrum antibiotics.

Info Box

Evidence as of March 2021 suggests that bacterial co-infection occurs in less than about 8% of people with COVID-19, and could be as low as 0.1% in people in hospital with COVID-19. Viral and fungal co-infections occur at lower rates than bacterial co-infections.

Secondary infection or co-infection (bacterial, viral or fungal) is more likely the longer a person is in hospital and the more they are immunosuppressed (for example, because of certain types of treatment).

The type and number of secondary infections or co-infections will vary depending on the season and any restrictions in place (for example, lockdowns).

8.4.1 Identifying secondary bacterial pneumonia

Consensus recommendation

In hospitals or other acute delivery settings (for example, virtual wards), to help identify non-SARS-CoV-2 viral, fungal or bacterial pneumonia, and to inform decision making about using antibiotics, consider the following tests:

- a full blood count
- chest imaging (X-ray, CT or ultrasound)
- respiratory and blood samples (for example, sputum or a tracheal aspirate sample, blood culture; see [Public Health England's COVID-19: guidance for sampling and for diagnostic laboratories](#))
- urine samples for legionella and pneumococcal antigen testing
- throat samples for respiratory viral (and atypical pathogen) polymerase chain reaction testing.

Info Box

High C-reactive protein levels do not necessarily indicate whether pneumonia is due to bacteria or SARS-CoV-2.

Low C-reactive protein level indicates that a secondary bacterial infection is less likely.

Consensus recommendation

Do not use C-reactive protein to assess whether a person has a secondary bacterial infection if they have been having immunosuppressant treatment.

Info Box

There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about antibiotics. Centres already using procalcitonin tests are encouraged to participate in research and data collection.

Procalcitonin tests could be useful in identifying whether there is a bacterial infection. However, it is not clear whether they add benefit beyond what is suggested in the [recommendation on tests to help differentiate between viral and bacterial pneumonia to guide decisions about antibiotics](#). The most appropriate threshold for procalcitonin is also uncertain.

8.4.2 Antibiotic treatment in the community

Consensus recommendation

Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.

Consensus recommendation

If a person has suspected or confirmed secondary bacterial pneumonia, start antibiotic treatment as soon as possible. Take into account any different methods needed to deliver medicines during the COVID-19 pandemic (see the [recommendation on minimising face-to-face contact in communication and shared decision making](#)).

Info Box

For antibiotic choices to treat community-acquired pneumonia caused by a secondary bacterial infection, see the recommendations on choice of antibiotic in the [NICE antimicrobial prescribing guideline on community-acquired pneumonia](#).

Consensus recommendation

Advise people to seek medical help without delay if their symptoms do not improve as expected, or worsen rapidly or significantly, whether they are taking an antibiotic or not.

Consensus recommendation

On reassessment, reconsider whether the person has signs and symptoms of more severe illness (see the [recommendation on signs and symptoms to help identify people with COVID-19 with the most severe illness](#)) and whether to refer them to hospital, other acute community support services or palliative care services.

8.4.3 Starting antibiotics in hospital

Consensus recommendation

Start empirical antibiotics if there is clinical suspicion of a secondary bacterial infection in people with COVID-19. When a decision to start antibiotics has been made:

- start empirical antibiotic treatment as soon as possible after establishing a diagnosis of secondary bacterial pneumonia, and certainly within 4 hours
- start treatment within 1 hour if the person has suspected sepsis and meets any of the high-risk criteria for this outlined in the [NICE guideline on sepsis](#).

8.4.4 Choice of antibiotics in hospital

Info Box

To guide decision making about antibiotics for secondary bacterial pneumonia in people with COVID-19, see the [NICE guideline on pneumonia \(hospital acquired\): antimicrobial prescribing](#).

Consensus recommendation

When choosing antibiotics, take account of:

- local antimicrobial resistance data and
- other factors such as their availability.

Consensus recommendation

Give oral antibiotics if the person can take oral medicines and their condition is not severe enough to need intravenous antibiotics.

Consensus recommendation

Consider seeking specialist advice on antibiotic treatment for people who:

- are immunocompromised
- have a history of infection with resistant organisms
- have a history of repeated infective exacerbations of lung disease
- are pregnant
- are receiving advanced respiratory support or organ support.

Consensus recommendation

Seek specialist advice if:

- there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic or
- there is clinical or microbiological evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.

8.4.5 Reviewing antibiotic treatment in hospital

Consensus recommendation

Review all antibiotics at 24 to 48 hours, or as soon as test results are available. If appropriate, switch to a narrower spectrum antibiotic, based on microbiological results.

For intravenous antibiotics, review within 48 hours and think about switching to oral antibiotics (in line with the [NICE guideline on pneumonia \(hospital-acquired\): antimicrobial prescribing](#))

Give antibiotics for 5 days, and then stop them unless there is a clear indication to continue (see the [recommendation on when to seek specialist advice](#)).

Consensus recommendation

Reassess people if their symptoms do not improve as expected, or worsen rapidly or significantly.

8.4.6 Ongoing review of co-infections in people with COVID-19

Info Box

We are currently reviewing new evidence on co-infections in people with COVID-19 as part of a living guidelines approach. New and updated recommendations will be published for this guideline as they become available (see [Update information | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE](#)).

9. Discharge, follow up and rehabilitation

Info Box

NICE is monitoring evidence on follow up, discharge and rehabilitation. Recommendations will be added in a future version of the guideline.

Info Box

For follow up and rehabilitation for people who have either ongoing symptomatic COVID-19 or post-COVID-19 syndrome, see the [NICE guideline on the long-term effects of COVID-19](#).

10. Palliative care

10.1 Principles of care



Info Box

For people who are nearing the end of their life, see:

- The [NICE guideline on care of dying adults in the last days of life](#): this includes recommendations on recognising when a person may be in the last days of life, communication and shared decision making.
- The [NICE guideline on end of life care for adults: service delivery](#): this includes recommendations for service providers on systems to help identify adults who may be at the end of their life, providing information and advanced care planning.
- The [NICE guideline on care and support of people growing older with learning disabilities](#): this includes recommendations on accessing end-of-life care services, person-centred care, and involving families and support networks in end-of-life care planning.

10.2 Medicines for end-of-life care



Consensus recommendation

Consider an opioid and benzodiazepine combination. See the table in practical info for managing breathlessness in the last days and hours of life for people 18 years and over with COVID-19 who:

- are at the end of life and
- have moderate to severe breathlessness and
- are distressed.

Consider concomitant use of an antiemetic and a regular stimulant laxative. Seek specialist advice for children and young people under 18 years.



Info Box

For more recommendations on pharmacological interventions and anticipatory prescribing, see the [NICE guideline on care of dying adults in the last days of life](#) and prescribing information in the [BNF's prescribing in palliative care](#).



Consensus recommendation

For people with COVID-19 who are out of hospital, when prescribing and supplying anticipatory medicines at the end of life:

- Take into account potential waste, medicines shortages and lack of administration equipment by prescribing smaller quantities or by prescribing a different medicine, formulation or route of administration when appropriate.
- If there are fewer health and care staff, you may need to prescribe subcutaneous, rectal or long-acting formulations. Family members could be considered as an alternative option to administer medications if they so wish and have been provided with appropriate training.



Consensus recommendation

For people with COVID-19 who are out of hospital, consider different routes for administering medicines if the person is unable to take or tolerate oral medicines, such as sublingual or rectal routes, subcutaneous injections or continual subcutaneous infusions.

11. Research recommendations

What is the effectiveness and safety of standard-dose compared with intermediate-dose pharmacological venous thromboembolism (VTE) prophylaxis for people with COVID-19, with or without additional risk factors for VTE?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over being treated for COVID-19 pneumonia in hospital or the community who have:

- no additional risk factors for VTE
- additional risk factors for VTE

I: intermediate dose:

- low molecular weight heparins (LMWH)
- unfractionated heparin (UFH)
- fondaparinux sodium
- direct-acting anticoagulant
- vitamin K antagonists

C: Standard-dose:

- LMWH
- UFH
- fondaparinux sodium
- direct-acting anticoagulants
- vitamin K antagonists
- antiplatelets

O:

- incidence of VTE
- mortality (all-cause, inpatient, COVID-19 related)
- admission to critical care (including use of advanced organ support)
- serious adverse events such as major bleeding or admission to hospital

What is the effectiveness and safety of extended pharmacological venous thromboembolism (VTE) prophylaxis for people who have been discharged after treatment for COVID-19?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over who have been discharged after treatment for COVID-19 pneumonia

I: extended (2 to 6 weeks) pharmacological VTE prophylaxis with standard-dose:

- low molecular weight heparins
- unfractionated heparins
- fondaparinux sodium
- direct-acting anticoagulant
- vitamin K antagonists

C: No extended pharmacological VTE prophylaxis

O:

- incidence of VTE
- mortality (all-cause, inpatient, COVID-19 related)
- serious adverse events such as major bleeding or admission to hospital

☐ What is the effectiveness and safety of a treatment dose with a low molecular weight heparin (LMWHs) compared with a standard prophylactic dose for venous thromboembolism (VTE) prophylaxis in young people under 18 years with COVID-19?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 18 years and under who have COVID-19 pneumonia

I: treatment-dose LMWH

C: standard prophylaxis with LMWH

O:

- incidence of VTE
- mortality (all-cause, inpatient, COVID-19 related)
- admission to critical care (including use of advanced organ support)
- serious adverse events such as major bleeding or admission to hospital

☐ Does early review and referral to specialist palliative care services improve outcomes for adults with COVID-19 thought to be approaching the end of their life?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients with a confirmed diagnosis of COVID-19 in hospital or community approaching the last days of life

I: early referral to specialist palliative care services (for example, in the last days of life)

C: late referral (for example, within the final day of life) or no referral

O:

- quality of life
- changes to clinical care
- patient or carer satisfaction (feeling supported)
- identification and/or achievement of patient wishes such as preferred place of death

☐ Is high-flow nasal oxygen effective in reducing breathlessness compared with standard care or conventional oxygen therapy for people in hospital with COVID-19 and respiratory failure when it is agreed that treatment will not be escalated beyond non-invasive respiratory support or palliative care is needed?

Remark:

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: adults over 18 years with COVID-19 having treatment for respiratory failure

I: high-flow nasal oxygen

C:

- standard care
- conventional oxygen therapy

O:

- patient experience
- symptom improvement
- frequency of coughing
- assessment of breathing pattern disorder
- impact of breathlessness on activities of daily living such as eating, drinking and movement
- recovery of sense of smell
- practicalities of maintaining high-flow nasal oxygen at home for patients who wish their end of life care to occur at home.

Subgroups: palliative care

☐ Does a multidisciplinary team agreed approach to weaning from continuous positive airway pressure improve weaning times and result in stopping continuous positive airway pressure for people with COVID-19 and acute respiratory failure?

Remark:

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people with COVID-19 having continuous positive airway pressure for respiratory support

I: multidisciplinary team agreed approach to weaning

C:

- standard care
- different multidisciplinary team approaches

O:

- patient experience
- symptom improvement
- length of time to wean



Updated

What is the effectiveness, cost effectiveness and safety of using a combination of casirivimab and imdevimab at doses other than 8 g for treating COVID-19?

Remark:

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people hospitalised because of COVID-19

I: treatment with different doses of casirivimab and imdevimab

C:

- recommended dose against different doses
- standard care against recommended dose and/or different doses

O:

- mortality
- progression to invasive mechanical ventilation
- progression to non-invasive respiratory support
- duration of hospitalisation
- adverse events
- costs of treatment
- health-related quality of life



Updated

What is the effectiveness, cost effectiveness and safety of the combination of casirivimab and imdevimab for treating COVID-19 in people with particular clinical characteristics (for example, people who are seropositive, of unknown serostatus, immunocompromised, or with specific comorbidities and within both the seropositive and seronegative groups, according to vaccination status or history of natural infection)?

Remark:

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people hospitalised because of COVID-19

I: treatment with a combination of casirivimab and imdevimab

C:

- treatment in people with different clinical characteristics (for example, people who are seropositive, of unknown serostatus, immunocompromised, or with specific comorbidities and within both the seropositive and seronegative groups, according to vaccination status or history of natural infection)

O:

- mortality
- progression to invasive mechanical ventilation
- progression to non-invasive respiratory support
- duration of hospitalisation
- adverse events
- costs of treatment
- health-related quality of life



New

What is the clinical and cost effectiveness of budesonide for treating COVID-19 in the community in adults, young people and children?

Remark:

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: Adults, young people and children who have COVID-19 and are not in hospital

Subgroups of particular interest:

- People 18 to 49 years
- Children and young people

I: Inhaled budesonide

C: Inhaled placebo (to accommodate blinding)

O:

- All-cause mortality
- Hospitalisation
- Need for oxygen therapy (including thresholds for this decision)
- Costs of treatment
- Time to recovery
- Health-related quality of life
- Adverse events

12. Equality considerations

12.1 Equalities impact assessment during scoping - draft scope

12.2 Equalities impact assessment during scoping - final scope

12.3 Equalities impact assessment during guideline development

13. Methods and processes

1. How to use this guideline

In response to the COVID-19 pandemic, NICE produced multiple rapid guidelines to support the health and social care system. We know that having different products can make it difficult for people trying to find guidance, so we have brought together NICE's published recommendations on managing COVID-19 into this single guideline. We hope users will find the content easier to find and use.

Many of the recommendations made early in the pandemic were based on the consensus of the guideline expert panels, so supporting information is limited. We have reviewed all content, using topic expert input and more recent evidence, and updated the recommendations where needed.

We aim to update these recommendations frequently in line with new evidence and will produce new recommendations where gaps are identified. We search and sift the evidence weekly to produce living recommendations that reflect the latest best available evidence.

We have developed this guideline using our [methods and processes for guidelines developed during health and social care emergencies](#). For more details of the methods and processes used for this guideline, including details of the expert advisory panel members, see the [methods and processes section](#).

Using the guideline in MAGICapp

The guideline consists of 2 layers: recommendations and supporting information.

1. Recommendations

Recommendation for (Green)

A strong recommendation is given when there is high-certainty evidence, or lower-certainty evidence paired with consistent panel expertise, showing that the overall benefits of the intervention are clearly greater than the disadvantages. This means that all, or nearly all, patients will want the recommended intervention.

Recommendation against (Red)

A strong recommendation against the intervention is given when there is high-certainty evidence, or lower-certainty evidence paired with important contextual factors, showing that the overall disadvantages of the intervention are clearly greater than the benefits, or that the intervention is not effective. A strong recommendation is also used when the examination of the evidence shows that an intervention is not safe.

Conditional Recommendation for (Yellow)

A conditional recommendation is given when it is considered that the benefits of the intervention are greater than the disadvantages, or the available evidence cannot rule out a significant benefit of the intervention while assessing that the adverse effects are few or absent. This recommendation is also used when patient preferences vary.

Conditional Recommendation against (Orange)

A conditional recommendation is given against the intervention when it is judged that the intervention may not be effective, but certainty is low. This recommendation is also used where the intervention is not likely to be effective, but it may be useful in specific settings or populations. Likewise, it is also used when patient preferences vary.

Only in research settings

A recommendation only for research settings is given where there is significant uncertainty about the effectiveness of an intervention, and it is not clear whether the benefits of the intervention are greater than the disadvantages or adverse effects.

Consensus Recommendation (Bluish-Purple)

A consensus recommendation can be given for or against an intervention, or may outline good practice or steps required to support other recommendations. This type of recommendation is used when there is not enough evidence to give an evidence-based recommendation, but the panel still regards it as important to give a recommendation.

2. Supporting information

Click on the recommendation to learn more about the basis of the recommendation. As stated, supporting information is limited

for recommendations created early in the pandemic. Additional information will be added as recommendations are updated in light of new evidence.

Recommendations will have supporting information in some or all of the following areas:

Research evidence: The overall effect estimates and references to the studies.

Certainty of the evidence:

- **High:** We are very sure that the true effect is close to the estimated effect.
- **Moderate:** We are moderately sure of the estimated effect. The true effect is probably close to this one, but there is a possibility that it is statistically significantly different.
- **Low:** We have limited confidence in the estimated effect. The true effect may be statistically significantly different from the estimated effect.
- **Very low:** We have very little confidence in the estimated effect. The true effect is likely to be statistically significantly different from the estimated effect.

Evidence to decision: Brief description of beneficial and harmful effects, certainty of evidence and considerations of patient preferences.

Rationale: Description of how the panel reached its decision.

Practical information: Practical information about the treatment and information on any special patient considerations.

Adaption: If a recommendation has been adapted from another guideline, this will provide further details.

Feedback: If you are logged in as a user, you can use the 'Feedback' option to comment on specific recommendations.

References: Reference list for the recommendation.

2. Introduction

Scope and purpose

This guideline is for health and care practitioners, and those involved in planning and delivering services. It provides guidance on managing COVID-19. The guideline makes recommendations about care in all settings for adults, children and young people with clinically diagnosed or laboratory-confirmed COVID-19.

Key questions

This section lists the key questions that the guideline addresses. These are a broad set of overarching review questions. Through our living approach, we will review the scope, and develop more specific review questions to address gaps in content and, where needed, additional review questions.

- What investigations should be carried out, and when, to determine the appropriate management of COVID-19 and any complications?
- What is the clinical effectiveness and safety of pharmacological and non-pharmacological treatments for acute symptoms and complications of COVID-19?
- How should symptoms and complications be managed?
- How, and how often, should people with COVID-19 be followed up?
- What palliative and end-of-life strategies are effective for people with COVID-19?

Areas to be excluded

The following areas are outside of the scope of this guideline and we will not look at evidence in these areas:

- procuring and distributing medicines and technologies, including vaccines
- procuring, distributing and using personal protective equipment
- procuring and distributing COVID-19 tests
- frequency of staff testing for COVID-19.

Acknowledgement

This work was done by NICE. The views expressed in this publication are those of the authors. We collaborated with the [Australian National COVID-19 Clinical Evidence Taskforce](#) based at Cochrane Australia, in the School of Population Health and Preventive Medicine at Monash University, to ensure appropriate development of the guideline, and acknowledge their contribution to identifying and reviewing the evidence for therapeutics.

3. Definition of disease severity

COVID-19 disease severity definitions are outlined in the [World Health Organization's COVID-19 clinical management living guidance](#).

4. Communication and shared decision making

Consensus recommendation

Communicate with people with COVID-19, and their families and carers, and support their mental wellbeing to help alleviate any anxiety and fear they may have. Signpost to charities and support groups (including NHS Volunteer Responders), to [NHS every mind matters](#) and to [Royal College of Paediatrics and Child Health resources for parents and carers](#).

Give people information in a way that they can use and understand, to help them take part in decisions about their care. Follow relevant national guidance on communication, providing information (including in different formats and languages) and shared decision making, for example, [NICE's guideline on patient experience in adult NHS services](#).

The [Royal College of Obstetricians and Gynaecologists](#) has produced information on COVID-19 and pregnancy for pregnant women and their families.

Consensus recommendation

For adults with COVID-19, explain:

- that the typical symptoms are cough, fever, and loss of sense of smell or taste, but that they may also have breathlessness (which may cause anxiety), delirium (which may cause agitation), fatigue, headache, muscle aches and sore throat
- that other symptoms may be drowsiness (particularly in older people), poor appetite, and chest discomfort or pain
- that they and people in close contact with them or in the same household (including those caring for them) should follow [Public Health England's stay at home: guidance for households with possible or confirmed coronavirus \(COVID-19\) infection](#) and the [UK government guidance on protecting vulnerable people](#)
- that they are likely to feel much better in a week if their symptoms are mild
- who to contact if their symptoms get worse, for example, [NHS 111 online](#).

Consensus recommendation

For carers of people with COVID-19 who should isolate but are unable to (for example, people with dementia), signpost to relevant support and resources.

For example, the [Alzheimer's Society](#) has information on staying safe from coronavirus and reducing the risk of infection.

Consensus recommendation

For children and young people under 18 years with COVID-19, explain:

- that additional symptoms (to those found in adults) may include grunting, nasal flare, nasal congestion, poor appetite, gastrointestinal symptoms, skin rash and conjunctivitis
- that they and people in close contact with them or in the same household (including those caring for them) should follow [Public Health England's stay at home: guidance for households with possible or confirmed coronavirus \(COVID-19\) infection](#)
- that they are likely to feel much better in a week if their symptoms are mild
- who to contact if their symptoms get worse, for example, [NHS 111 online](#)
- that the presence of fever, rash, abdominal pain, diarrhoea or vomiting may indicate paediatric inflammatory multisystem syndrome (PIMS)
- how and when to seek medical help if PIMS is suspected.

Consensus recommendation

In the community, consider the risks and benefits of face-to-face and remote care for each person. Where the risks of face-to-face care outweigh the benefits, remote care can be optimised by:

- offering telephone or video consultations (see [BMJ guidance on Covid-19: a remote assessment in primary care](#) for a useful guide, including a [visual summary for remote consultation](#))
- cutting non-essential face-to-face follow up
- using electronic prescriptions rather than paper
- using different methods to deliver medicines to people, for example, pharmacy deliveries, postal services and NHS volunteers, or introducing drive-through pick-up points for medicines.

Consensus recommendation

When possible, discuss the risks, benefits and possible likely outcomes of the treatment options with people with COVID-19, and their families and carers. Use decision support tools (when available).

This will help people express their preferences about their treatment and escalation plans. Bear in mind that these discussions may need to take place remotely.

Consensus recommendation

For people with pre-existing advanced comorbidities, find out if they have advance care plans or advance decisions to refuse treatment, including do not attempt cardiopulmonary resuscitation decisions. Document this clearly and take account of these in planning care.

5. Assessment

5.1 In the community

5.1.1 Identifying severe COVID-19

Consensus recommendation

Use the following signs and symptoms to help identify people with COVID-19 with the most severe illness:

- severe shortness of breath at rest or difficulty breathing
- reduced oxygen saturation levels measured by pulse oximetry (see the [recommendation on pulse oximetry levels that indicate serious illness](#))
- coughing up blood
- blue lips or face
- feeling cold and clammy with pale or mottled skin
- collapse or fainting (syncope)
- new confusion
- becoming difficult to rouse
- reduced urine output.

For signs and symptoms to help identify paediatric inflammatory multisystem syndrome (PIMS) temporarily associated with COVID-19, see the [guidance on PIMS from the Royal College of Paediatrics and Child Health](#).

Consensus recommendation

When pulse oximetry is available in primary and community care settings, to assess the severity of illness and detect early deterioration, use:

- [NHS England's guide to pulse oximetry](#) in people 18 years and over with COVID-19
- oxygen saturation levels below 91% in room air at rest in children and young people (17 years and under) with COVID-19.

Be aware that different pulse oximeters have different specifications, and that some can under- or overestimate readings especially if the saturation level is borderline. Overestimation has been reported in people with dark skin.

Rationale

This recommendation is based on the expert panel's consensus view. The panel agreed that using pulse oximetry to measure oxygen saturation threshold levels is appropriate for helping to identify people with acute COVID-19 in primary or community care, and to predict outcomes such as hospitalisation. NHS England has guidance on pulse oximetry in assessment in adults in the community. The panel agreed that it is appropriate to cross-refer to this guidance for adults but not for children. The panel's recommended oxygen saturation level for children and young people was based on their consensus view that oxygen saturation levels below 91% in room air at rest are appropriate to assess the severity of illness and detect early deterioration in this group.

Info Box

Assessing shortness of breath (dyspnoea) is important, but may be difficult via remote consultation. Tools such as the [Medical Research Council's dyspnoea scale](#) or the [Centre for Evidence Based Medicine's review of ways of assessing dyspnoea \(breathlessness\) by telephone or video](#) can be useful.

The [NEWS2 tool](#) may be used in adults in addition to clinical judgment to assess a person's risk of deterioration. Note that use of [NEWS2](#) is not advised in children or pregnant women. Although the NEWS2 tool is not validated for predicting the risk of clinical deterioration in prehospital settings, it may be a helpful adjunct to clinical judgement in adults. A face-to-face consultation should not be arranged solely to calculate a NEWS2 score.

Locally approved Paediatric Early Warning Scores should be used for children. When using early warning scores, ensure that readings are based on calibrated machines. Be aware that readings may be incomplete when doing remote consultations.

Consensus recommendation

For people with severe respiratory symptoms associated with COVID-19 (for example, suspected pneumonia) being managed in the community, see the [recommendation on venous thromboembolism in hospital-led acute care in the community](#).

5.1.2 Care planning

Consensus recommendation

Discuss with people with COVID-19, and their families and carers, the benefits and risks of hospital admission or other acute care delivery services (for example, virtual wards or hospital at home teams).

Some benefits and risks may be similar for all patients (for example, improved diagnostic tests and access to treatments, or better contact with families in the community), but others may be personal to the individual (such as loss of access to carers who can anticipate needs well in someone unable to communicate themselves, or risks of spreading COVID-19).

Consensus recommendation

Explain that people with COVID-19 may deteriorate rapidly. Discuss future care preferences at the first assessment to give people who do not have existing advance care plans an opportunity to express their preferences.

5.2 In hospital

Consensus recommendation

When a person is admitted to hospital with COVID-19, ensure a holistic assessment is done, including discussion about their treatment expectations and care goals:

- Document and assess the stability of underlying health conditions, involving relevant specialists as needed.
- Use the Clinical Frailty Scale (CFS) when appropriate, available from the NHS Specialised Clinical Frailty Network, to assess baseline health and inform discussions on treatment expectations.
- Use the CFS within an individualised assessment of frailty.
- Do not use the CFS for younger people, people with stable long-term disabilities (for example, cerebral palsy), learning disabilities or autism. Make an individualised assessment of frailty in these people, using clinical assessment and alternative scoring methods.
- Record the assessment and discussion in the person's medical records.

For assessment of paediatric inflammatory multisystem syndrome (PIMS), follow the [guidance on PIMS from the Royal College of Paediatrics and Child Health](#).

Consensus recommendation

When making decisions about the care of children and young people under 18 years, people with learning disabilities or adults who lack mental capacity for health decision making, for example, people with advanced dementia, see the [NICE guideline on decision-making and mental capacity](#).

Ensure discussions on significant care interventions involve families and carers as appropriate, and local experts or advocates.

6. Management

6.1 In the community

6.1.1 Care planning

Consensus recommendation

Put treatment escalation plans in place in the community after sensitively discussing treatment expectations and care goals with people with COVID-19, and their families and carers.

People with COVID-19 may deteriorate rapidly. If it is agreed that the next step is a move to secondary care, ensure that they and their families understand how to access this with the urgency needed. If the next step is other community-based support (whether virtual wards, hospital at home services or palliative care), ensure that they and their families understand how to access these services, both in and out of hours.

6.1.2 Managing cough

Consensus recommendation

Encourage people with cough to avoid lying on their backs, if possible, because this may make coughing less effective.

Be aware that older people or those with comorbidities, frailty, impaired immunity or a reduced ability to cough and clear secretions are more likely to develop severe pneumonia. This could lead to respiratory failure and death.

Consensus recommendation

Use simple measures first, including advising people over 1 year with cough to take honey.

The dose is 1 teaspoon of honey.

Consensus recommendation

Consider short-term use of codeine linctus, codeine phosphate tablets or morphine sulfate oral solution in people 18 years and over to suppress coughing if it is distressing. Seek specialist advice for people under 18 years.

See practical info for dosages for treatments to manage cough in people 18 years and over.

Practical Info

Treatments for managing cough in people 18 years and over

Treatment	Dosage
Initial management: use simple non-drug measures, for example, taking honey	A teaspoon of honey
First choice, only if cough is distressing: codeine linctus (15 mg/5 ml) or codeine phosphate tablets (15 mg, 30 mg)	15 mg to 30 mg every 4 hours as required, up to 4 doses in 24 hours If necessary, increase dose to a maximum of 30 mg to 60 mg four times a day (maximum 240 mg in 24 hours)
Second choice, only if cough is distressing: morphine sulfate oral solution (10 mg/5 ml)	2.5 mg to 5 mg when required every 4 hours Increase up to 5 mg to 10 mg every 4 hours as required If the person is already taking regular morphine increase the regular dose by a third

Notes: See the [BNF](#) and [MHRA advice](#) for appropriate use and dosage in specific populations.

All doses are for oral administration.

Consider the addiction potential of codeine linctus, codeine phosphate and morphine sulfate. Issue as an 'acute' prescription with a limited supply. Advise the person of the risks of constipation and consider prescribing a regular stimulant laxative.

Avoid cough suppressants in chronic bronchitis and bronchiectasis because they can cause sputum retention.

6.1.3 Managing fever

Consensus recommendation

Advise people with COVID-19 and fever to drink fluids regularly to avoid dehydration. Support their families and carers to help when appropriate. Communicate that fluid intake needs can be higher than usual because of fever.

Consensus recommendation

Advise people to take paracetamol or ibuprofen if they have fever and other symptoms that antipyretics would help treat. Tell them to continue only while both the symptoms of fever and the other symptoms are present.

People can take paracetamol or ibuprofen when self-medicating for symptoms of COVID-19, such as fever (see the [Central Alerting System: novel coronavirus - anti-inflammatory medications](#) for further details of ibuprofen including dosage).

For people 18 years and over, the paracetamol dosage is 1 g orally every 4 to 6 hours (maximum 4 g per day). See the [BNF](#) and [Medicines and Healthcare products Regulatory Agency advice](#) for appropriate use and dosage in specific adult populations.

For children and young people over 1 month and under 18 years, see the dosing information on the pack or the [BNF for children](#).

Rectal paracetamol, if available, can be used as an alternative. For rectal dosage information, see the [BNF](#) and [BNF for children](#).

6.1.4 Managing breathlessness

Consensus recommendation

Identify and treat reversible causes of breathlessness, for example, pulmonary oedema, pulmonary embolism, chronic obstructive pulmonary disorder and asthma.

For further information on identifying and managing pulmonary embolism, see the [NICE guideline on venous thromboembolic diseases: diagnosis, management and thrombophilia testing](#).

Consensus recommendation

When significant medical pathology has been excluded or further investigation is inappropriate, the following may help to manage breathlessness as part of supportive care:

- keeping the room cool
- encouraging relaxation and breathing techniques, and changing body positioning
- encouraging people who are self-isolating alone to improve air circulation by opening a window or door.

If hypoxia is the likely cause of breathlessness:

- consider a trial of oxygen therapy
- discuss with the person, their family or carer possible transfer to and evaluation in secondary care.

Breathlessness with or without hypoxia often causes anxiety, which can then increase breathlessness further.

6.1.5 Managing anxiety, delirium and agitation

Consensus recommendation

Assess reversible causes of delirium. See the [NICE guidance on delirium: prevention, diagnosis and management](#).

Consensus recommendation

Address reversible causes of anxiety by:

- exploring the person's concerns and anxieties
- explaining to people providing care how they can help.

Consensus recommendation

Consider trying a benzodiazepine to manage anxiety or agitation. See practical info for treatments for managing anxiety, delirium and agitation in people 18 years and over. Seek specialist advice for people under 18 years.

Practical Info

Treatments for managing anxiety, delirium and agitation in people 18 years and over

Treatment	Dosage
Anxiety or agitation and able to swallow: lorazepam tablets	Higher doses may be needed for symptom relief in people with COVID-19. Lower doses may be needed because of the person's size or frailty The doses are based on the BNF and the Palliative care formulary Lorazepam 0.5 mg to 1 mg four times a day as required (maximum 4 mg in 24 hours) Reduce the dose to 0.25 mg to 0.5 mg in older people or those who are debilitated (maximum 2 mg in 24 hours) Oral tablets can be used sublingually (off-label use)
Anxiety or agitation and unable to swallow: midazolam injection	Midazolam 2.5 mg to 5 mg by subcutaneous injection every 2 to 4 hours as required If needed frequently (more than twice daily), a subcutaneous infusion via a syringe

Treatment	Dosage
Delirium and able to swallow: haloperidol tablets	<p>driver may be considered (if available) starting with midazolam 10 mg over 24 hours</p> <p>Reduce dosage to 5 mg over 24 hours if estimated glomerular filtration rate is less than 30 ml per minute</p> <p>Haloperidol 0.5 mg to 1 mg at night and every 2 hours when required. Increase dose in 0.5 mg to 1 mg increments as required (maximum 10 mg daily, or 5 mg daily in older people)</p> <p>The same dose of haloperidol may be administered by subcutaneous injection as required rather than orally, or as a subcutaneous infusion of 2.5 mg to 10 mg over 24 hours</p> <p>Consider a higher starting dose (1.5 mg to 3 mg) if the person is severely distressed or causing immediate danger to others</p> <p>Consider adding a benzodiazepine such as lorazepam or midazolam if the person remains agitated (see dosages above)</p> <p>Levomepromazine 12.5 mg to 25 mg as a subcutaneous injection as a starting dose and then hourly as required (use 6.25 mg to 12.5 mg in older people)</p>
Delirium and unable to swallow: levomepromazine injection	<p>Maintain with a subcutaneous infusion of 50 mg to 200 mg over 24 hours, increased according to response (doses greater than 100 mg over 24 hours should be given under specialist supervision)</p> <p>Consider midazolam alone or in combination with levomepromazine if the person also has anxiety (see dosages above)</p> <p>Special considerations</p> <p>Seek specialist advice for people under 18 years old</p>

Notes: At the time of publication (March 2021), midazolam and levomepromazine did not have a UK marketing authorisation for this indication or route of administration (see the [General Medical Council's guidance on prescribing unlicensed medicines](#) for further information).

See the [BNF](#) and [MHRA advice](#) for appropriate use and dosing in specific populations.

6.1.6 Managing medicines

Consensus recommendation

When supporting people with symptoms of COVID-19 who are having care in the community delivered by social care, follow the [NICE guideline on managing medicines for adults receiving social care in the community](#). This includes processes for ordering and supplying medicines, and transporting, storing and disposing of medicines.

Consensus recommendation

When prescribing, handling, administering and disposing of medicines in care homes and hospices follow the [NICE guideline on managing medicines in care homes](#) and the [UK government COVID-19 standard operating procedure for running a medicines re-use scheme in a care home or hospice setting](#).

6.2 In hospital

6.2.1 Deciding when to escalate treatment

Consensus recommendation

Base decisions about escalating treatment within the hospital on the likelihood of a person's recovery. Take into account their treatment expectations, goals of care and the likelihood that they will recover to an outcome that is acceptable to them.

For support with decision making, see:

- [advice on ethics from the British Medical Association](#)
- [ethical guidance from the Royal College of Physicians](#)
- [national guidance presented by the Faculty of Intensive Care Medicine, Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists](#)
- [advice on decision making under pandemic conditions by the Intensive Care Society, and](#)
- [advice on decision making and consent from the General Medical Council](#)

Consensus recommendation

Ensure healthcare professionals have access to resources to support discussions about treatment plans (see, for example, [decision-making for escalation of treatment and referring for critical care support](#), and an example [decision support form](#)).

Tools such as the [British Medical Journal emergency care and resuscitation plan](#) may be useful when making decisions about a treatment plan.

Consensus recommendation

Discuss treatment escalation with a multidisciplinary team of medical and allied health professional colleagues (such as from critical care, respiratory medicine, geriatric medicine and palliative care) when there is uncertainty about treatment escalation decisions.

Consensus recommendation

Document referral to and advice from critical care services and respiratory support units in a standard format. When telephone advice from critical care or respiratory support units is appropriate, this should still be documented in a standard format (see [an example of a tool for documentation](#)).

6.2.2 Escalating and de-escalating treatment

Consensus recommendation

Before escalating respiratory or other organ support, identify agreed treatment goals with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate). Start all advanced respiratory support or organ support with a clear plan of how it will address the diagnosis and lead to agreed treatment goals (outcomes). Ensure this includes management plans for when there is further deterioration or no response to treatment.

Do not continue respiratory or other organ support if it is considered that it will no longer result in the desired overall goals (outcomes). Record the decision and the discussion with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate).

6.2.3 Delivering services in critical care and respiratory support units

Consensus recommendation

Trusts should review:

- their strategy on management for people who are deteriorating and
- use of the track-and-trigger system (NEWS2 has been endorsed by NHS England and Improvement).

See the [NICE guideline on acutely ill adults in hospital for recommendations on identifying patients whose clinical condition is deteriorating or is at risk of deterioration](#).

See the [Royal College of Physician's information on the place of NEWS2 in managing patients with COVID-19](#).

6.2.4 Non-invasive respiratory support

Info Box

Definitions

High-flow nasal oxygen (HFNO): involves the delivery of warm and humidified oxygen (up to 60 litres per minute) through a small nasal cannula. The delivered flow is higher than the flow of air when the person is breathing in (inspiratory flow). HFNO can also deliver a higher concentration of oxygen than supplemental oxygen alone.

Continuous positive airway pressure (CPAP): is a type of positive airway pressure that delivers a set pressure of airflow to the airways. This pressure is maintained throughout the respiratory cycle, both when the person is breathing in (inspiration) and breathing out (expiration). A CPAP device consists of a unit that generates airflow, which is delivered to the airway through a tight-fitting mask or other airtight interface.

Non-invasive ventilation (NIV): refers to a mode of positive pressure ventilation that delivers airflow to the airways through a tight-fitting mask or other airtight interface. Airflow is delivered at variable pressures that are higher than when the person is breathing in (inspiratory pressure) and lower than when the person is breathing out (expiratory pressure).

Non-invasive respiratory support: is a broad umbrella term for different types of non-invasive respiratory support, such as HFNO, CPAP and NIV. They are considered to be a more intensive intervention than oxygen therapy alone. The different types of support are not, however, interchangeable with each other because they have differing effects on a person's physiology. So, they typically have different indications for their use.

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the [Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'](#).

Info Box

For information on deciding when to escalate and de-escalate treatment, see the [sections on deciding when to escalate treatment](#) and [escalating and de-escalating treatment](#). Also, consider factors such as:

- how much supplemental oxygen is needed to reach target oxygen saturation
- the overall clinical trajectory
- assessment of work of breathing
- how well treatment will be tolerated
- treatment preferences after discussion with the person, and their family and carers when appropriate.

The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy.

Info Box

For information on how to manage COVID-19 in people who are having non-invasive respiratory support, see the [sections on management](#) and [therapeutics for COVID-19](#).

Consensus recommendation

Ensure that pharmacological and non-pharmacological management strategies, including body positioning, are optimised before escalating treatment to non-invasive respiratory support.

The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy.

Evidence To Decision

Benefits and harms

The panel discussed the findings from the 2 randomised controlled trials (Recovery-RS and HENIVOT) included in the evidence review.

There is no evidence on optimising pharmacological and non-pharmacological management strategies before starting non-invasive respiratory support, but the panel noted that this is an important consideration. They made a consensus recommendation to optimise medical management (including pharmacological and non-pharmacological treatment) before starting non-invasive respiratory support.

Rationale

Based on their experience, the panel highlighted the importance of ensuring that existing management, including body positioning, is optimised before respiratory support is escalated.

Conditional recommendation against

Do not routinely offer high-flow nasal oxygen as the main form of respiratory support for people with COVID-19 and respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate.

Evidence To Decision**Benefits and harms**

Small net benefit, or little difference between alternatives

The panel discussed the findings from the 2 randomised controlled trials (Recovery-RS and HENIVOT) included in the evidence review.

They noted that evidence from the Recovery-RS trial does not show that using high-flow nasal oxygen (HFNO) has any benefits compared with conventional oxygen therapy. They made a recommendation to not routinely offer HFNO as the main form of respiratory support for people with respiratory failure due to COVID-19 in whom escalation to invasive mechanical ventilation would be appropriate.

The panel agreed that the evidence from the Recovery-RS trial shows that using continuous positive airway pressure (CPAP) reduces the number of people who need invasive ventilation and admission to critical care. Evidence from the HENIVOT trial shows that helmet non-invasive ventilation followed by HFNO significantly reduces the number of people who need invasive ventilation compared with HFNO alone. They also noted that evidence from the Recovery-RS trial suggests there is a small increase in the number of serious adverse events with CPAP compared with conventional oxygen therapy. However, they considered that there are uncertainties with the available evidence, including evidence on standard care, staffing ratios, and where people had CPAP and which staff gave it. The panel agreed that these uncertainties warranted a recommendation to consider offering CPAP for people with COVID-19 when they:

- have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 40% to 60%, and
- would be suitable for escalation to invasive mechanical ventilation but it is not immediately needed.

The panel noted that it is important for staff to have skills and competencies in CPAP and that people have CPAP in an appropriate setting. They provided a consensus recommendation to support this.

The panel discussed the importance of ensuring that CPAP is not used for longer than it is needed. They strongly emphasised the importance of regularly reviewing people having CPAP (for example every 12 hours) to ensure that it is promptly recognised when treatment has failed and that treatment is escalated when needed. They made a consensus recommendation to support this. The panel agreed not to define treatment failure to allow for individual clinical decision making.

The panel also made a consensus recommendation to optimise medical management (including pharmacological and non-pharmacological treatment) before starting non-invasive respiratory support.

Certainty of the Evidence

Low

The panel were aware that the certainty of the evidence for outcomes in the Recovery-RS trial and HENIVOT trial ranged from moderate to low and low to very low, respectively. They also noted that the Recovery-RS trial is currently only available as a pre-print publication. This means that the results have not been peer reviewed, so the panel interpreted the results with the appropriate caution.

Preference and values

No substantial variability expected

Lay members noted that people with COVID-19 may have different opinions on how acceptable non-invasive respiratory support is. Some people may be apprehensive of its use and others may be willing to accept it as an available treatment option. Patient preferences should be considered in a shared discussion.

The panel agreed that treatment plans, preferences and wishes should be discussed with patients, families and carers before starting non-invasive respiratory support. For this reason, information boxes linking to the existing guideline recommendations on escalation and de-escalation of treatment have been provided. The panel also considered that care of people who will not have care escalated should be supported by provision of an information box linking to existing recommendations on pharmacological and non-pharmacological treatment options.

The panel noted that outcomes, such as symptom control, would be important to people with COVID-19 and should be reported in future trials. The panel proposed to make a research recommendation to explore if high-flow nasal oxygen reduces breathlessness compared with standard care or conventional oxygen therapy to help improve the evidence base in this area.

Resources

No important issues with the recommended alternative

The panel considered that using continuous positive airway pressure (CPAP) for people with COVID-19 in appropriate settings outside of the intensive care unit (ICU) has the potential to free up ICU capacity. Avoiding the need for invasive mechanical ventilation may also result in cost savings and avoid adverse outcomes from intubation. However, the panel were mindful that CPAP should be given by staff who have skills and competencies in CPAP and be accompanied by careful review and prompt recognition of when treatment has failed and further treatment escalation is needed.

Cost effectiveness was not assessed as part of the evidence review.

Equity

Important issues, or potential issues not investigated

The scope of this evidence review was limited to adults and so no evidence in children and young people was included.

The panel noted that some people, including those with learning disabilities, dementia or delirium for example, may find it difficult to tolerate non-invasive respiratory support. As such, patient preferences should be considered in a shared discussion with the person and their family or carer.

Acceptability

Important issues, or potential issues not investigated

The panel discussed that some people can find that continuous positive airway pressure (CPAP) is uncomfortable. The panel commented that some people may find it difficult to tolerate non-invasive respiratory support. They noted that using high-flow nasal oxygen would allow people having CPAP to take treatment breaks for mealtimes and when CPAP is being gradually reduced. They made a consensus recommendation to support this. The panel proposed a research recommendation to explore which treatment methods are effective for weaning people with COVID-19 from CPAP and the acceptability and safety of these methods.

Feasibility

Important issues, or potential issues not investigated

Continuous positive airway pressure (CPAP) and high-flow nasal oxygen are established treatments in the NHS. However, the panel advised that context-specific factors influence when CPAP is used, for example staff skills and competencies, staffing ratios and the availability of different CPAP interfaces, so CPAP use may vary in practice.

Rationale

Evidence from a clinical trial does not show that high-flow nasal oxygen has treatment benefits over conventional oxygen therapy for people in whom escalation to invasive mechanical ventilation would be appropriate. So, the panel agreed that it

should not be used as the preferred treatment option in this situation.

The panel acknowledged that although high-flow nasal oxygen should not be offered as the main form of respiratory support routinely, it may be considered when people having continuous positive airway pressure (CPAP) need a break from CPAP, for example at mealtimes, or when they are being weaned from CPAP or when they need humidified oxygen.

Clinical Question/ PICO

Population:	People with COVID-19
Intervention:	CPAP
Comparator:	Conventional oxygen

Summary

Evidence indicates that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?

Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics

One RCT included adult (≥ 18 -years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO₂) of 94% or below despite receiving a fraction of inspired oxygen (FiO₂) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Grieco 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?

Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of

intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	Study results and measurements	Comparator Conventional oxygen	Intervention CPAP	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 30 days	Odds Ratio 0.91 (CI 95% 0.59 – 1.39) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ¹	One study found no statistically significant difference in mortality with CPAP compared with conventional oxygen in people with COVID-19.
Tracheal intubation or mortality 30 days	Odds Ratio 0.67 (CI 95% 0.48 – 0.94) (Randomized controlled)			Moderate Due to serious risk of bias ²	One study found a statistically significant reduction in the composite outcome of tracheal intubation or mortality with CPAP compared with conventional oxygen in people with COVID-19.

Outcome Timeframe	Study results and measurements	Comparator Conventional oxygen	Intervention CPAP	Certainty of the Evidence (Quality of evidence)	Plain language summary
Intubation 30 days	Odds Ratio 0.66 (CI 95% 0.47 – 0.93) (Randomized controlled)			Moderate Due to serious risk of bias ³	One study found a statistically significant reduction in intubation with CPAP compared with conventional oxygen in people with COVID-19.
Median time to intubation	Hazard Ratio 0.67 (CI 95% 0.52 – 0.86) (Randomized controlled)			Moderate Due to serious risk of bias ⁴	One study found a statistically significant difference in median time to intubation with CPAP compared with conventional oxygen in people with COVID-19.
Admission to critical care	Odds Ratio 0.69 (CI 95% 0.49 – 0.96) (Randomized controlled)			Moderate Due to serious risk of bias ⁵	One study found a statistically significant reduction in admission to critical care with CPAP compared with conventional oxygen in people with COVID-19.
Mean length of stay in hospital (days)	Lower better (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ⁶	One study found no statistically significant difference in length of hospital stay with CPAP compared with conventional oxygen in people with COVID-19.
Mean length of stay in critical care (days)	Lower better (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ⁷	One study found no statistically significant difference in length of critical care stay with CPAP compared with conventional oxygen in people with COVID-19.

1. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
2. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
4. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias,

inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

7. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

Clinical Question/ PICO

Population: People with COVID-19
Intervention: HFNO
Comparator: Conventional oxygen

Summary

Evidence indicates that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?

Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics

One RCT included adult (≥ 18 -years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO₂) of 94% or below despite receiving a fraction of inspired oxygen (FiO₂) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Grieco 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?

Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	Study results and measurements	Comparator Conventional oxygen	Intervention HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 30 days	Odds Ratio 0.96 (CI 95% 0.64 – 1.45) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ¹	One study found no statistically significant difference in mortality with HFNO compared with conventional oxygen in people with COVID-19.

Outcome Timeframe	Study results and measurements	Comparator Conventional oxygen	Intervention HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
Tracheal intubation or mortality 30 days	Odds Ratio 0.95 (CI 95% 0.69 – 1.3) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ²	One study found no statistically significant difference in the composite outcome of tracheal intubation or mortality with HFNO compared with conventional oxygen in people with COVID-19.
Intubation 30 days	Odds Ratio 0.96 (CI 95% 0.7 – 1.31) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ³	One study found no statistically significant difference in intubation with HFNO compared with conventional oxygen in people with COVID-19.
Median time to intubation	Hazard Ratio 0.91 (CI 95% 0.72 – 1.14) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ⁴	One study found no statistically significant difference in intubation with HFNO compared with conventional oxygen in people with COVID-19.
Admission to critical care	Odds Ratio 1.06 (CI 95% 0.76 – 1.47) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ⁵	One study found no statistically significant difference in admission to critical care with HFNO compared with conventional oxygen in people with COVID-19.
Mean length of stay in hospital (days)	Lower better (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ⁶	One study found no statistically significant difference in length of hospital stay with HFNO compared with conventional oxygen in people with COVID-19.
Mean length of stay in critical care (days)	Lower better (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ⁷	One study found no statistically significant difference in length of hospital stay with HFNO compared with conventional oxygen in people with COVID-19.

1. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

2. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias,

inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crossed line of no effect. **Publication bias: no serious.**

3. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

4. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

5. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

7. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

Clinical Question/ PICO

Population: People with COVID-19
Intervention: Helmet non-invasive ventilation followed by HFNO
Comparator: HFNO

Summary

Evidence indicates that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?

Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics

One RCT included adult (≥ 18 -years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO₂) of 94% or below despite receiving a fraction of inspired oxygen (FiO₂) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Greico 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?

Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Greico 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	Study results and measurements	Comparator HFNO	Intervention Helmet non- invasive ventilation following by HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality at 28 days	Relative risk 0.81 (CI 95% 0.35 – 1.91) Based on data from 109 patients in 1 studies. ¹ (Randomized controlled)	182 per 1000 Difference:	147 per 1000 35 fewer per 1000 (CI 95% 118 fewer – 166 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ²	One study found no statistically significant difference in mortality with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Mortality at 60 days	Relative risk 1.1 (CI 95% 0.55 – 2.2) Based on data from 109 patients in 1 studies. ³ (Randomized controlled)	218 per 1000 Difference:	240 per 1000 22 more per 1000 (CI 95% 98 fewer – 262 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ⁴	One study found no statistically significant difference in mortality with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
In-hospital mortality	Relative risk 0.95 (CI 95% 0.49 – 1.82) Based on data from 109 patients in 1 studies. ⁵ (Randomized controlled)	255 per 1000 Difference:	242 per 1000 13 fewer per 1000 (CI 95% 130 fewer – 209 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ⁶	One study found no statistically significant difference in in-hospital mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
In-intensive care unit mortality	Relative risk 0.8 (CI 95% 0.4 – 1.6) Based on data from 109 patients in 1 studies. ⁷ (Randomized controlled)	255 per 1000 Difference:	204 per 1000 51 fewer per 1000 (CI 95% 153 fewer – 153 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ⁸	One study found no statistically significant difference in intensive care mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Intubation within 28 days from enrolment	Relative risk 0.58 (CI 95% 0.36 – 0.95) Based on data from 109 patients in 1 studies. ⁹ (Randomized controlled)	509 per 1000 Difference:	295 per 1000 214 fewer per 1000 (CI 95% 326 fewer – 25 fewer more)	Low Due to serious risk of bias, due to serious indirectness ¹⁰	One study found a statistically significant reduction in intubation with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Intubation within 28 days from enrolment after adjudication of	Relative risk 0.55 (CI 95% 0.33 – 0.9) Based on data from 109 patients in 1 studies. ¹¹ (Randomized controlled)	509 per 1000 Difference:	280 per 1000 229 fewer per 1000	Low Due to serious risk of bias, Due to serious indirectness ¹²	One study found a statistically significant reduction in intubation with helmet non- invasive ventilation followed by HFNO

Outcome Timeframe	Study results and measurements	Comparator HFNO	Intervention Helmet non- invasive ventilation following by HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
intubation criteria by external experts			(CI 95% 341 fewer – 51 fewer)		compared with HFNO in people with COVID-19.
Respiratory support free days	High better (Randomized controlled)	18 (Median) Difference:	20 (Median) MD 2 more (CI 95% 2 fewer – 6 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ¹³	One study found no statistically significant difference in respiratory support free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Invasive ventilation free days 28 days	High better (Randomized controlled)	25 (Median) Difference:	28 (Median) MD 3 more (CI 95% 0 more – 7 more)	Low Due to serious risk of bias, Due to serious indirectness ¹⁴	One study found a statistically significant increase in invasive ventilation free days with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Invasive ventilation free days 60 days	High better (Randomized controlled)	57 (Median) Difference:	60 (Median) MD 6 more (CI 95% 3 fewer – 15 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ¹⁵	One study found no statistically significant difference in invasive ventilation free days with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Duration of hospital stay (days)	Lower better (Randomized controlled)	22 days (Median) Difference:	21 days (Median) MD 6 fewer (CI 95% 14 fewer – 1 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ¹⁶	One study found no statistically significant difference in duration of hospital stay with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Duration of ICU stay (days)	Lower better (Randomized controlled)	10 (Median) Difference:	9 (Median) MD 6 fewer (CI 95% 13 fewer – 1 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ¹⁷	One study found no statistically significant difference in duration of ICU stay with helmet non-invasive ventilation followed by HFNO compared with HFNO

Outcome Timeframe	Study results and measurements	Comparator HFNO	Intervention Helmet non- invasive ventilation following by HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
					in people with COVID-19.

1. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
3. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
5. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
7. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
9. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
11. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
13. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
15. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence

interval crosses line of no effect. **Publication bias: no serious.**

16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.

Inconsistency: no serious. Indirectness: serious. due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

17. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.

Inconsistency: no serious. Indirectness: serious. due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

References

86. Respiratory support for COVID-19.

Conditional recommendation

Consider offering continuous positive airway pressure (CPAP) to people with COVID-19 when:

- they have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 0.4 (40%) or more, **and**
- escalation to invasive mechanical ventilation would be an option but it is not immediately needed, **or**
- it is agreed that respiratory support should not be escalated beyond CPAP.

In June 2021, the [Medicines and Healthcare products Regulatory Agency issued a National Patient Safety Alert for Philips ventilator, CPAP and bilevel positive airway pressure devices](#) because of a potential for harm from inhaled particles and volatile organic compounds. This applies to all devices manufactured before 26 April 2021.

For information on decision making and giving advice, see the [British Thoracic Society risk stratification guidance on Philips ventilator, CPAP and bilevel positive airway pressure devices](#).

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel discussed the findings from the 2 randomised controlled trials (Recovery-RS and HENIVOT) included in the evidence review.

They noted that evidence from the Recovery-RS trial does not show that using high-flow nasal oxygen (HFNO) has any benefits compared with conventional oxygen therapy. They made a recommendation to not routinely offer HFNO as the main form of respiratory support for people with respiratory failure due to COVID-19 in whom escalation to invasive mechanical ventilation would be appropriate.

The panel agreed that the evidence from the Recovery-RS trial shows that using continuous positive airway pressure (CPAP) reduces the number of people who need invasive ventilation and admission to critical care. Evidence from the HENIVOT trial shows that helmet non-invasive ventilation followed by HFNO significantly reduces the number of people who need invasive ventilation compared with HFNO alone. They also noted that evidence from the Recovery-RS trial suggests there is a small increase in the number of serious adverse events with CPAP compared with conventional oxygen therapy. However, they considered that there are uncertainties with the available evidence, including evidence on standard care, staffing ratios, and where people had CPAP and which staff gave it. The panel agreed that these uncertainties warranted a recommendation to consider offering CPAP to people with COVID-19 when they:

- have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 40% to 60%,

and

- would be suitable for escalation to invasive mechanical ventilation but is not immediately needed.

The panel noted that it is important for staff to have skills and competencies in CPAP and that people have CPAP in an appropriate setting. They provided a consensus recommendation to support this.

The panel discussed the importance of ensuring that CPAP is not used for longer than it is needed. They strongly emphasised the importance of regularly reviewing people having CPAP (for example every 12 hours) to ensure that it is promptly recognised when treatment has failed and that treatment is escalated when needed. They made a consensus recommendation to support this. The panel agreed not to define treatment failure to allow for individual clinical decision making.

The panel also made a consensus recommendation to optimise medical management (including pharmacological and non-pharmacological treatment) before starting non-invasive respiratory support.

Certainty of the Evidence

Low

The panel were aware that the certainty of the evidence for outcomes in the Recovery-RS trial and HENIVOT trial ranged from moderate to low and low to very low, respectively. They also noted that the Recovery-RS trial is currently only available as a pre-print publication. This means that the results have not been peer reviewed, so the panel interpreted the results with the appropriate caution.

Preference and values

No substantial variability expected

Lay members noted that people with COVID-19 may have different opinions on how acceptable non-invasive respiratory support is. Some people may be apprehensive of its use and others may be willing to accept it as an available treatment option. Patient preferences should be considered in a shared discussion.

The panel agreed that treatment plans, preferences and wishes should be discussed with patients, families and carers before starting non-invasive respiratory support. For this reason, information boxes linking to the existing guideline recommendations on escalation and de-escalation of treatment have been provided. The panel also considered that care of people who will not have treatment escalation should be supported by provision of an information box linking to existing recommendations on pharmacological and non-pharmacological treatment options.

The panel noted that outcomes, such as symptom control, would be important to people with COVID-19 and should be reported in future trials. The panel proposed to make a research recommendation to explore if high-flow nasal oxygen reduces breathlessness compared with standard care or conventional oxygen therapy to help improve the evidence base in this area.

Resources

No important issues with the recommended alternative

The panel considered that using continuous positive airway pressure (CPAP) for people with COVID-19 in appropriate settings outside of the intensive care unit (ICU) has the potential to free up ICU capacity. Avoiding the need for invasive mechanical intubation may also result in cost savings and avoid adverse outcomes from intubation. However, the panel were mindful that CPAP should be given by staff who have skills and competencies in CPAP, and be accompanied by careful review and prompt recognition of when treatment has failed and further treatment escalation is needed.

Cost effectiveness was not assessed as part of the evidence review.

Equity

Important issues, or potential issues not investigated

The scope of this evidence review was limited to adults and so no evidence in children and young people was included.

The panel noted that some people, including those with learning disabilities, dementia or delirium for example, may find it difficult to tolerate non-invasive respiratory support. As such, patient preferences should be considered in a shared discussion with the person and their family or carer.

Acceptability

Important issues, or potential issues not investigated

The panel discussed that some people find that continuous positive airway pressure (CPAP) is uncomfortable. The panel commented that some people may find it difficult to tolerate non-invasive respiratory support. They noted that high-flow nasal oxygen would allow people having CPAP to take treatment breaks for mealtimes and when CPAP is being gradually reduced. They made a consensus recommendation to support this. The panel proposed a research recommendation to explore which treatment methods are effective for weaning people with COVID-19 from CPAP and the acceptability and safety of these methods.

Feasibility

Important issues, or potential issues not investigated

Continuous positive airway pressure (CPAP) and high-flow nasal oxygen are established treatments in the NHS. However, the panel advised that context-specific factors influence when CPAP may be used, for example staff skills and competencies, staffing ratios and the availability of different CPAP interfaces, so CPAP use may vary in practice.

Rationale

Evidence from a clinical trial suggests that there may be some treatment benefits with continuous positive airway pressure for people who have hypoxaemia and in whom escalation to invasive mechanical ventilation would be an option, particularly for intubation outcomes (including likelihood of requiring tracheal intubation and invasive mechanical ventilation). But, this is uncertain.

Clinical Question/ PICO

Population:	People with COVID-19
Intervention:	CPAP
Comparator:	Conventional oxygen

Summary

Evidence indicates that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?

Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics

One RCT included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute

respiratory failure, defined as peripheral oxygen saturations (SpO₂) of 94% or below despite receiving a fraction of inspired oxygen (FiO₂) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Grieco 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?

Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	Study results and measurements	Comparator Conventional oxygen	Intervention CPAP	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 30 days	Odds Ratio 0.91 (CI 95% 0.59 – 1.39) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ¹	One study found no statistically significant difference in mortality with CPAP compared with conventional oxygen in people with COVID-19.
Tracheal intubation or mortality 30 days	Odds Ratio 0.67 (CI 95% 0.48 – 0.94) (Randomized controlled)			Moderate Due to serious risk of bias ²	One study found a statistically significant reduction in the composite outcome of tracheal intubation or mortality with CPAP compared with conventional oxygen in people with COVID-19.
Intubation 30 days	Odds Ratio 0.66 (CI 95% 0.47 – 0.93) (Randomized controlled)			Moderate Due to serious risk of bias ³	One study found a statistically significant reduction in intubation with CPAP compared with conventional oxygen in people with COVID-19.
Median time to intubation	Hazard Ratio 0.67 (CI 95% 0.52 – 0.86) (Randomized controlled)			Moderate Due to serious risk of bias ⁴	One study found a statistically significant difference in median time to intubation with CPAP compared with conventional oxygen in people with COVID-19.
Admission to critical care	Odds Ratio 0.69 (CI 95% 0.49 – 0.96) (Randomized controlled)			Moderate Due to serious risk of bias ⁵	One study found a statistically significant reduction in admission to critical care with CPAP compared with conventional oxygen in people with COVID-19.
Mean length of stay in hospital (days)	Lower better (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ⁶	One study found no statistically significant difference in length of hospital stay with CPAP compared with conventional oxygen in people with COVID-19.
		17.3 days (Mean)	16.4 days (Mean)		
		Difference:	MD 0.97 fewer (CI 95% 3.65 fewer – 1.71 more)		

Outcome Timeframe	Study results and measurements	Comparator Conventional oxygen	Intervention CPAP	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mean length of stay in critical care (days)	Lower better (Randomized controlled)	9.6 (Mean) Difference:	9.5 (Mean) MD 0.33 fewer (CI 95% 2.44 fewer – 1.78 more)	Low Due to serious risk of bias, Due to serious imprecision ⁷	One study found no statistically significant difference in length of critical care stay with CPAP compared with conventional oxygen in people with COVID-19.

1. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
2. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
4. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
7. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

Clinical Question/ PICO

Population: People with COVID-19
Intervention: HFNO
Comparator: Conventional oxygen

Summary

Evidence indicates that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?

Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics

One RCT included adult (≥ 18 -years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO₂) of 94% or below despite receiving a fraction of inspired oxygen (FiO₂) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Grieco 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?

Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or

mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	Study results and measurements	Comparator Conventional oxygen	Intervention HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 30 days	Odds Ratio 0.96 (CI 95% 0.64 – 1.45) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ¹	One study found no statistically significant difference in mortality with HFNO compared with conventional oxygen in people with COVID-19.
Tracheal intubation or mortality 30 days	Odds Ratio 0.95 (CI 95% 0.69 – 1.3) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ²	One study found no statistically significant difference in the composite outcome of tracheal intubation or mortality with HFNO compared with conventional oxygen in people with COVID-19.
Intubation 30 days	Odds Ratio 0.96 (CI 95% 0.7 – 1.31) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ³	One study found no statistically significant difference in intubation with HFNO compared with conventional oxygen in people with COVID-19.
Median time to intubation	Hazard Ratio 0.91 (CI 95% 0.72 – 1.14) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ⁴	One study found no statistically significant difference in intubation with HFNO compared with conventional oxygen in people with COVID-19.
Admission to critical care	Odds Ratio 1.06 (CI 95% 0.76 – 1.47) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ⁵	One study found no statistically significant difference in admission to critical care with HFNO compared with conventional oxygen in

Outcome Timeframe	Study results and measurements	Comparator Conventional oxygen	Intervention HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
					people with COVID-19.
Mean length of stay in hospital (days)	Lower better (Randomized controlled)	17.1 (Mean) Difference:	18.3 (Mean) MD 0.7 more (CI 95% 1.93 fewer – 3.34 more)	Low Due to serious risk of bias, Due to serious imprecision ⁶	One study found no statistically significant difference in length of hospital stay with HFNO compared with conventional oxygen in people with COVID-19.
Mean length of stay in critical care (days)	Lower better (Randomized controlled)	9.5 (Mean) Difference:	10.5 (Mean) MD 0.69 more (CI 95% 1.37 fewer – 2.75 more)	Low Due to serious risk of bias, Due to serious imprecision ⁷	One study found no statistically significant difference in length of hospital stay with HFNO compared with conventional oxygen in people with COVID-19.

- Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
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Clinical Question/ PICO

Population: People with COVID-19

Intervention: Helmet non-invasive ventilation followed by HFNO
Comparator: HFNO

Summary

Evidence indicates that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?

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The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

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- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics

One RCT included adult (≥ 18 -years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO₂) of 94% or below despite receiving a fraction of inspired oxygen (FiO₂) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Grieco 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?

Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results*Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)*

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	Study results and measurements	Comparator HFNO	Intervention Helmet non- invasive ventilation following by HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality at 28 days	Relative risk 0.81 (CI 95% 0.35 – 1.91) Based on data from 109 patients in 1 studies. ¹ (Randomized controlled)	182 per 1000 Difference:	147 per 1000 35 fewer per 1000 (CI 95% 118 fewer – 166 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ²	One study found no statistically significant difference in mortality with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Mortality at 60 days	Relative risk 1.1 (CI 95% 0.55 – 2.2) Based on data from 109 patients in 1 studies. ³ (Randomized controlled)	218 per 1000 Difference:	240 per 1000 22 more per 1000 (CI 95% 98 fewer – 262 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ⁴	One study found no statistically significant difference in mortality with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
In-hospital mortality	Relative risk 0.95 (CI 95% 0.49 – 1.82) Based on data from 109 patients in 1 studies. ⁵ (Randomized controlled)	255 per 1000 Difference:	242 per 1000 13 fewer per 1000	Very low Due to serious risk of bias, Due to serious imprecision, Due	One study found no statistically significant difference in in-hospital mortality with helmet non-invasive ventilation followed by HFNO

Outcome Timeframe	Study results and measurements	Comparator HFNO	Intervention Helmet non- invasive ventilation following by HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
			(CI 95% 130 fewer – 209 more)	to serious indirectness ⁶	compared with HFNO in people with COVID-19.
In-intensive care unit mortality	Relative risk 0.8 (CI 95% 0.4 – 1.6) Based on data from 109 patients in 1 studies. ⁷ (Randomized controlled)	255 per 1000 Difference:	204 per 1000 51 fewer per 1000 (CI 95% 153 fewer – 153 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ⁸	One study found no statistically significant difference in intensive care mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Intubation within 28 days from enrolment	Relative risk 0.58 (CI 95% 0.36 – 0.95) Based on data from 109 patients in 1 studies. ⁹ (Randomized controlled)	509 per 1000 Difference:	295 per 1000 214 fewer per 1000 (CI 95% 326 fewer – 25 fewer)	Low Due to serious risk of bias, due to serious indirectness ¹⁰	One study found a statistically significant reduction in intubation with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Intubation within 28 days from enrolment after adjudication of intubation criteria by external experts	Relative risk 0.55 (CI 95% 0.33 – 0.9) Based on data from 109 patients in 1 studies. ¹¹ (Randomized controlled)	509 per 1000 Difference:	280 per 1000 229 fewer per 1000 (CI 95% 341 fewer – 51 fewer)	Low Due to serious risk of bias, Due to serious indirectness ¹²	One study found a statistically significant reduction in intubation with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Respiratory support free days	High better (Randomized controlled)	18 (Median) Difference:	20 (Median) MD 2 more (CI 95% 2 fewer – 6 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ¹³	One study found no statistically significant difference in respiratory support free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Invasive ventilation free days 28 days	High better (Randomized controlled)	25 (Median) Difference:	28 (Median) MD 3 more (CI 95% 0 more – 7 more)	Low Due to serious risk of bias, Due to serious indirectness ¹⁴	One study found a statistically significant increase in invasive ventilation free days with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with

Outcome Timeframe	Study results and measurements	Comparator HFNO	Intervention Helmet non- invasive ventilation following by HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
					COVID-19.
Invasive ventilation free days 60 days	High better (Randomized controlled)	57 (Median) Difference:	60 (Median) MD 6 more (CI 95% 3 fewer – 15 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ¹⁵	One study found no statistically significant difference in invasive ventilation free days with helmet non- invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Duration of hospital stay (days)	Lower better (Randomized controlled)	22 days (Median) Difference:	21 days (Median) MD 6 fewer (CI 95% 14 fewer – 1 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ¹⁶	One study found no statistically significant difference in duration of hospital stay with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Duration of ICU stay (days)	Lower better (Randomized controlled)	10 (Median) Difference:	9 (Median) MD 6 fewer (CI 95% 13 fewer – 1 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness ¹⁷	One study found no statistically significant difference in duration of ICU stay with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.

1. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
3. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
5. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
7. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.

8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
9. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
11. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
13. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
15. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
17. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

References

86. Respiratory support for COVID-19.

Consensus recommendation

For people with COVID-19 having continuous positive airway pressure, ensure:

- there is access to critical care providers for advice, review and prompt escalation of treatment if needed (such as when treatment has failed)
- regular review by an appropriate senior clinician (such as every 12 hours) and more frequent review if needed, in line with the British Thoracic Society guidance on respiratory support units and the Faculty of Intensive Care Medicine guidelines on the provision of intensive care services
- regular assessment and management of symptoms alongside non-invasive respiratory support.

Staff caring for people with COVID-19 having CPAP should have appropriate skills and competencies and provide appropriate monitoring. For further information on standards of care and provision of services see the [Faculty of Intensive Care Medicine and Intensive Care Society guidelines on the provision of intensive care services](#) and the [British Thoracic Society and Intensive Care Society guidance on development and implementation of respiratory support units](#).

Evidence To Decision**Benefits and harms**

The panel discussed the findings from the 2 randomised controlled trials (Recovery-RS and HENIVOT) included in the evidence review.

There is no evidence on reviewing and monitoring people having continuous positive airway pressure (CPAP). However, the panel noted that it is important that staff have skills and competencies in CPAP and that people have CPAP in an appropriate setting. They provided a consensus recommendation to support this.

The panel also discussed the importance of ensuring that CPAP is not used for longer than it is needed. They strongly emphasised the importance of regularly reviewing people having CPAP (for example every 12 hours) to ensure that it is promptly recognised when treatment has failed and that treatment is escalated when needed. They made a consensus recommendation to support this.

Rationale

Based on their experience, the panel agreed that it is important to closely review people with COVID-19 having continuous positive airway pressure and recognise the need for escalation of treatment.

Consensus recommendation

Consider using high-flow nasal oxygen for people having continuous positive airway pressure (CPAP) when they need:

- a break from CPAP, such as at mealtimes
- humidified oxygen
- weaning from CPAP.

Evidence To Decision**Benefits and harms**

The panel discussed the findings from the 2 randomised controlled trials (Recovery-RS and HENIVOT) included in the evidence review.

Although there is no evidence on treatment breaks from continuous positive airway pressure (CPAP), the panel noted this was an important consideration. The panel discussed that people can find CPAP uncomfortable. The panel

commented that some people may find it difficult to tolerate non-invasive respiratory support. They noted that using high-flow nasal oxygen would allow people having CPAP to take breaks from treatment, for example at mealtimes and when CPAP is being gradually reduced. They made a consensus recommendation to support this.

Rationale

Based on their experience, the panel recognised that prolonged use of continuous positive airway pressure (CPAP) can be uncomfortable, and that there needs to be an appropriate alternative to CPAP when needed.

7. Therapeutics for COVID-19

7.1 Corticosteroids

Recommended

Offer dexamethasone, or either hydrocortisone or prednisolone when dexamethasone cannot be used or is unavailable, to people with COVID-19 who:

- need supplemental oxygen to meet their prescribed oxygen saturation levels or
- have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it.

Continue corticosteroids for up to 10 days unless there is a clear indication to stop early, which includes discharge from hospital or a hospital-supervised virtual COVID ward.

Being on a hospital-supervised virtual COVID ward is not classed as being discharged from hospital.

See Practical info for dosage information.

For full details of adverse events and contraindications, see the summaries of product characteristics.

For children with a greater than 44-week corrected gestational age, follow the [risk criteria set out in Royal College of Paediatric and Child Health guidance for assessing children admitted to hospital with COVID-19](#). For preterm babies with a corrected gestational age of less than 44 weeks, seek specialist advice.

Practical Info

Adult dosage

Dexamethasone:

- 6 mg orally once a day for 10 days (three 2 mg tablets or 15 ml of 2 mg/5 ml oral solution) or
- 6 mg intravenously once a day for 10 days (1.8 ml of 3.3 mg/ml ampoules [5.94 mg])

For people able to swallow and in whom there are no significant concerns about enteral absorption, prescribe tablets. Only use intravenous administration when tablets or oral solutions are inappropriate or unavailable.

Suitable alternatives:

- **Prednisolone:** 40 mg orally once a day for 10 days
- **Hydrocortisone:** 50 mg intravenously every 8 hours for 10 days (0.5 ml of 100 mg/ml solution; powder for solution for injection or infusion is also available); this may be continued for up to 28 days for people with septic shock

Dosage in pregnancy

Follow [Royal College of Obstetrics and Gynaecology guidance](#).

Dosage for children with a greater than 44-week corrected gestational age

- **Dexamethasone:** 150 micrograms/kg (as a base) orally, nasogastrically or intravenously once a day for 10 days (max 6 mg)
- **Prednisolone:** 1 mg/kg orally, nasogastrically or intravenously once a day for 10 days (max 40 mg; doses can be rounded as per routine clinical practice)

For people able to swallow and in whom there are no significant concerns about enteral absorption, prescribe tablets. Only use intravenous administration when tablets or oral solutions are inappropriate or unavailable.

Dosage for preterm babies with a corrected gestational age of less than 44 weeks

Seek specialist advice.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

For adults with COVID-19 needing supplemental oxygen, corticosteroids compared with usual care or placebo lower all-cause mortality, improve discharge from hospital, and may decrease the need for invasive mechanical ventilation (IMV) and death within 28 days of starting treatment.

For adults with COVID-19 not needing supplemental oxygen, corticosteroids may increase the need for IMV and death within 28 days of starting treatment.

Based on indirect evidence from non-COVID-19 populations, hyperglycaemia is the only statistically significant adverse event associated with corticosteroids.

Discussion

The panel noted the evidence to support using corticosteroids for adults with COVID-19 on supplemental oxygen, or adults with a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. They noted that it is now established standard practice to offer dexamethasone. This is based on the most robust evidence on corticosteroids covering this treatment, and its widespread availability, ease of administration and acceptable safety profile. The panel indicated that, if dexamethasone cannot be used or is unavailable, suitable alternatives are hydrocortisone or prednisolone. Because of the risk of harm, the panel cautioned against using corticosteroids for other people with COVID-19.

The panel noted the need for clear and unambiguous terminology. Therefore, they agreed that reference to COVID-19 severity would not be used. Instead, they agreed that a person's oxygen saturation should be used to determine whether corticosteroid treatment was appropriate. The panel highlighted the need to allow for varying prescribed oxygen saturation levels in different population groups. Because of this, they agreed that the recommendation should not detail specific oxygen saturation levels.

The course duration recommended, for up to 10 days unless there is a clear indication to stop early (including discharge from hospital or a hospital-supervised virtual COVID ward), is based on that used in the RECOVERY trial. The panel recognised the importance of minimising risk of harm caused by continuing treatment for people whose condition is improving and who are discharged. They agreed that the long pharmacodynamic half-life of dexamethasone would reduce the risk of any rebound effect caused by stopping the course before 10 days in the event of discharge. The panel agreed that, where patients are transferred to a virtual ward environment, the course could be completed safely under clinical supervision.

The panel acknowledged the lack of evidence outside the hospital setting. They also acknowledged that the supply and use of corticosteroids in other settings is based on clinical experience and knowledge of service delivery. It was the panel's opinion that, when corticosteroids are first started in community settings, GPs are suitably qualified to assess oxygen levels with pulse oximetry and the need for corticosteroids. They agreed that it is realistic that treatment with dexamethasone could be started in the community setting. They also agreed that the class effect of corticosteroids would allow for hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

Use of corticosteroids in children was considered. The panel decided that the recommendation should not be limited to adults because the evidence included both adults and children. The panel therefore agreed to avoid age-specific wording in the recommendation. Instead, they agreed that the dosing for adults and children should be provided as supplementary advice. Paediatric experts highlighted that the risk of progression for a child with a stable minimal oxygen requirement is not as high as for adults. Therefore, they suggested cross reference to Royal College of Child and Paediatric Health risk criteria markers for assessing corticosteroid use. For preterm babies with a corrected gestational age of less than 44 weeks, specialist advice is considered necessary because evidence is lacking for corticosteroid use in this age group.

The panel noted the indirect evidence about the risk of hyperglycaemia in other non-COVID-19 populations. They agreed that whether to monitor for hyperglycaemia and other adverse effects should be determined by their healthcare professionals, without the need for specific advice in the guideline. They added that potential adverse effects and contraindications would need to be balanced against the risks of depriving a person of a potentially life-saving treatment.

The panel considered that clinical judgement should guide management for people who do not need supplemental oxygen and who are already having corticosteroids for pre-existing or new comorbid conditions, without the need for specific

advice in the guideline.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for all-cause mortality within 28 days in both subgroups (adults needing oxygen, and adults not needing oxygen) because of serious imprecision (inconsistent direction of effects for studies of adults needing oxygen and only a single study for adults not needing oxygen). The panel noted that, despite serious imprecision, the pooled effect was statistically significantly in favour of corticosteroids for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of the evidence is moderate for invasive mechanical ventilation or death at 28 days in both subgroups because of serious imprecision (only a single study for both subgroups). The panel noted that, despite serious imprecision, the effect was statistically significantly in favour of dexamethasone for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of evidence is moderate for discharge from hospital in both subgroups because of serious imprecision (inconsistent confidence intervals for studies of adults needing oxygen and only a single study for adults not needing oxygen). However, the panel noted that, for adults with COVID-19 needing oxygen, there was a statistically significant effect in favour of corticosteroids for improving discharge from hospital at 28 days.

Certainty of evidence was moderate for serious adverse events of corticosteroids in adults with COVID-19 needing oxygen. The panel noted that corticosteroids probably have little effect on serious adverse events in this group of people, but were aware of indirect systematic review evidence showing a statistically significant risk of hyperglycaemia among people without COVID-19.

Certainty of evidence was low to moderate for other individual adverse effects, none of which showed statistically significant effects estimates.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences and values. The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who need oxygen, most would choose corticosteroids after shared decision making with healthcare professionals. Dexamethasone was considered to be the preferred corticosteroid treatment because of the larger amount of data supporting its use. The panel agreed that the class effect of corticosteroids would allow for hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

Resources

No important issues with the recommended alternative

Use of corticosteroids in adults with COVID-19 who are on supplemental oxygen is unlikely to affect the availability of these medicines for other indications.

The panel expressed concern over specifying oxygen therapy as a requirement for corticosteroid treatment in a recommendation. They agreed that this might result in inequalities in access to treatments because of certain groups of people not being able to have oxygen therapy, even though their oxygen saturations may indicate that they should. This may also result in supply issues in the event of oxygen shortages. The panel agreed that the emphasis should be on oxygen saturation targets for people who need oxygen supplementation.

The panel noted possible supply issues with corticosteroids in community pharmacies where people have treatment outside the hospital setting, such as in residential care. However, they agreed that GP assessment with pulse oximetry and treatment with dexamethasone is realistic in the community setting. The class effect of corticosteroids would allow for suitable alternatives. The panel acknowledged the lack of evidence outside the hospital setting. They also noted that the use and supply of corticosteroids in other settings is based on clinical experience and knowledge of service delivery.

Equity

Important issues, or potential issues not investigated

The panel noted limited evidence on the use of corticosteroids in children with COVID-19 but that children should not be excluded from the recommendations. The panel agreed that all age groups should be encompassed with appropriate age-specific advice on dosage.

The panel also noted the lack of evidence on the use of corticosteroids in community settings and the risk of inequitable treatment if limited to people in hospital. The panel were aware of people with COVID-19 needing supplemental oxygen who are having treatment outside the hospital setting and would benefit from corticosteroids. For this reason, the panel agreed that the recommendation should not specify any treatment setting.

See the Resources section for the panel's concern over potential inequality of access to corticosteroids if oxygen therapy is stated as a requirement for corticosteroid treatment, and the need for this to be reflected in the wording of the recommendation.

Acceptability

No important issues with the recommended alternative

The panel considered that acceptability of corticosteroids would be high given the widespread availability, ease of oral ingestion in any setting and established safety profile. They anticipated that, when considering the risks and benefits of treatment through shared decision making, most people with COVID-19 who:

- need supplemental oxygen would choose to have corticosteroids
- do not need supplemental oxygen would choose not to have corticosteroids.

Feasibility

No important issues with the recommended alternative

Although there is no systematically collected evidence about feasibility, the panel noted that the established distribution, supply and use of corticosteroids in clinical practice is an indicator of feasibility.

Rationale

There is evidence to support using corticosteroids for people with COVID-19 who need supplemental oxygen, or who have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. It is now established standard practice to offer dexamethasone. The growing evidence base, combined with its widespread availability, ease of administration and acceptable safety profile, supports its continued use. Hydrocortisone and prednisolone are suitable alternatives if dexamethasone cannot be used or is unavailable. The course duration recommended, for up to 10 days unless there is a clear indication to stop early (including discharge from hospital or a hospital-supervised virtual COVID ward), is based on that used in clinical trials.

Clinical Question/ PICO

Population:	People with COVID-19
Intervention:	Corticosteroids
Comparator:	Control

Summary

Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?

Evidence comes from a recent meta-analysis and associated living guidance [9] of seven randomised controlled trials (RCTs) of patients with critical COVID-19 [10][20][11][17][16][10][15], one study of patients with moderate, severe and critical COVID-19 [14], and one study of patients with severe COVID-19 [13]. Over 5,700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions – other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress [18] and sepsis [21] – provided indirect evidence for serious adverse events.

Study characteristics

Three RCTs compared dexamethasone with standard care [10][17][14], three compared hydrocortisone with standard care [16][11][12] and three compared methylprednisolone with standard care [20][15][13].

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation, $\text{PaO}_2/\text{FiO}_2 < 200$, positive end-expiratory pressure (PEEP) ≥ 5 cm H₂O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?

Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 RCTs). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and discharge from hospital within 28 days.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications showed no difference in the incidence of gastrointestinal bleeding, bacterial co-infections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 24 studies).

Our confidence in the results

In patients with COVID-19 requiring oxygen, certainty of the evidence is moderate for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect) and invasive mechanical ventilation or death (due to only one study), and discharge from hospital (due to serious inconsistency).

In patients with COVID-19 who do not require oxygen, certainty is moderate for all outcomes (all-cause mortality, invasive mechanical ventilation or death and discharge from hospital) due to serious imprecision (reliance on a single study and wide confidence intervals).

For the adverse events (gastrointestinal bleeding, super infections, neuromuscular weakness and neuropsychiatric effects), certainty is low due to serious indirectness (evidence from non-COVID-19 patients) and serious imprecision. For hyperglycaemia, certainty is moderate due to serious indirectness (evidence from non-COVID-19 patients).

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment	Relative risk 0.84 (CI 95% 0.73 – 0.98) Based on data from 5,789 patients in 9 studies. ¹ (Randomized controlled)	316 per 1000 Difference:	265 per 1000 51 fewer per 1000 (CI 95% 85 fewer	Moderate Due to some inconsistency ²	Nine studies found a statistically significantly lower incidence of all- cause mortality at day 28 with corticosteroids compared with standard care in adults who

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain language summary
9 Critical			— 6 fewer)		require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days of commencing treatment	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 patients in 1 studies. ³ (Randomized controlled)	140 per 1000 Difference:	178 per 1000 38 more per 1000 (CI 95% 0 fewer — 85 more)	Moderate Only data from one study	One study found no statistically significant difference in all cause mortality at day 28 with corticosteroids compared with placebo.
9 Critical					
Invasive mechanical ventilation or death [adults requiring oxygen] ⁴ Within 28 days of commencing treatment	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 patients in 1 studies. ⁵ (Randomized controlled)	320 per 1000 Difference:	282 per 1000 38 fewer per 1000 (CI 95% 67 fewer — 10 fewer)	Moderate Due to only one study	One study found a statistically significant reduction in death or the need for invasive mechanical ventilation at day 28 with corticosteroids compared with standard care in adults who require oxygen.
9 Critical					
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days of commencing treatment	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 patients in 1 studies. ⁶ (Randomized controlled)	155 per 1000 Difference:	194 per 1000 39 more per 1000 (CI 95% 0 fewer — 88 more)	Moderate Due to only one study ⁷	One study found no statistically significant reduction in death or the need for invasive mechanical ventilation at day 28 with corticosteroids compared with standard care in adults who do not require oxygen.
9 Critical					
Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 patients in 1 studies. ⁸ (Randomized controlled)	804 per 1000 Difference:	772 per 1000 32 fewer per 1000 (CI 95% 80 fewer — 8 more)	Moderate Due to only one study ⁹	One study found no statistically significant difference in discharge from hospital at day 28 with corticosteroids compared with standard care in adults who do not require oxygen.
9 Critical					
Discharge from hospital [adults requiring oxygen] Within 28 days of	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 patients in 2 studies. ¹⁰ (Randomized	582 per 1000 Difference:	640 per 1000 58 more per 1000	Moderate Due to serious inconsistency ¹¹	Two studies found a statistically significant increase in discharge from hospital at day 28 with corticosteroids

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain language summary
commencing treatment 9 Critical	controlled)		(CI 95% 35 more — 87 more)		compared with standard care in adults who require oxygen.
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 patients in 6 studies. ¹² (Randomized controlled)	234 per 1000 Difference:	187 per 1000 47 fewer per 1000 (CI 95% 110 fewer — 44 more)	Moderate Due to serious inconsistency ¹³	Six studies found no statistically significant difference in serious adverse events at day 28 with corticosteroids compared with standard care in adults who require oxygen.
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.82 — 1.33) Based on data from 5,403 patients in 30 studies.	48 per 1000 Difference:	51 per 1000 3 more per 1000 (CI 95% 9 fewer — 16 more)	Low Due to serious indirectness and imprecision	Thirty studies found no statistically significant difference in gastrointestinal bleeding with corticosteroids compared with standard care.
Bacterial co- infections End of treatment 6 Important	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 patients in 32 studies.	186 per 1000 Difference:	188 per 1000 2 more per 1000 (CI 95% 19 fewer — 24 more)	Low Due to serious indirectness and imprecision	Thirty two studies found no statistically significant difference in the incidence of bacterial coinfections with corticosteroids compared with standard care.
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 patients in 24 studies.	286 per 1000 Difference:	332 per 1000 46 more per 1000 (CI 95% 23 more — 72 more)	Moderate Due to serious indirectness	Twenty four studies found a statistically significant increase in the incidence of hyperglycaemia with corticosteroids compared with standard care.
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 patients in 8 studies.	69 per 1000 Difference:	75 per 1000 6 more per 1000 (CI 95% 10 fewer — 27 more)	Low Due to serious indirectness and imprecision	Eight studies found no statistically significant difference in the incidence of neuromuscular weakness with corticosteroids compared with standard care.
Neuropsychiatri c effects End of treatment	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 patients in 7 studies.	35 per 1000 Difference:	28 per 1000 7 fewer per 1000 (CI 95% 21 fewer	Low Due to serious indirectness and imprecision	Seven studies found no statistically significant difference in the incidence of neuropsychiatric effects with corticosteroids

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important			– 22 more)		compared with standard care.

1. Systematic review [9] with included studies: CoDEX 2020, REMAP-CAP 2020, CAPE COVID 2020, METCOVID 2020, Edalatifard 2020, RECOVERY, DEXA-COVID 19 2020, RECOVERY, COVID STEROID 2020, Steroids-SARI 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies.
3. Systematic review [9] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
4. Detailed description The number of patients with severe illness (i.e. who do not require mechanical ventilation at enrolment) that progress to requiring invasive mechanical ventilation or death within 28 days
5. Systematic review [9] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [9] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Imprecision: serious.** Only data from one study.
8. Systematic review [9] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Imprecision: serious.** Only data from one study.
10. Systematic review [9] with included studies: RECOVERY, RECOVERY, Edalatifard 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies..
12. Systematic review [9] with included studies: Steroids-SARI 2020, DEXA-COVID 19 2020, COVID STEROID 2020, REMAP-CAP 2020, CoDEX 2020, CAPE COVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies.

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Conditional recommendation against

Do not routinely use corticosteroids to treat COVID-19 in people who do not need supplemental oxygen, unless there is another medical indication to do so.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

For adults with COVID-19 needing supplemental oxygen, at 28 days, corticosteroids compared with usual care or placebo lower mortality, improve discharge from hospital, and may decrease the risk of needing invasive mechanical ventilation (IMV) and death.

For adults with COVID-19 not needing oxygen, corticosteroids may increase the risk of needing IMV and death within 28 days of starting treatment.

Based on indirect evidence from non-COVID-19 populations, hyperglycaemia is the only statistically significant adverse event associated with corticosteroids.

Discussion

The panel noted the evidence that corticosteroids may be harmful for people with COVID-19 not needing supplemental oxygen. Because of the risk of harm, the panel cautioned against using corticosteroids for people with COVID-19 not on oxygen unless there is another medical indication to do so.

The panel noted the need for clear and unambiguous terminology. Therefore, they agreed that reference to COVID-19 severity would not be used. Instead, they agreed that a person's oxygen saturation should be used to determine whether corticosteroid treatment was appropriate. The panel highlighted the need to allow for varying prescribed oxygen saturation levels in different population groups. Because of this, they agreed that the recommendation should not detail specific oxygen saturation levels.

The panel noted the indirect evidence about the risk of hyperglycaemia in other non-COVID-19 populations. They agreed that whether to monitor for hyperglycaemia and other adverse effects in individuals should be determined by their healthcare professionals, without the need for specific advice in the guideline. They added that potential adverse effects and contraindications would need to be balanced against the risks of depriving a person of a potentially life-saving treatment.

The panel considered that clinical judgement should guide management for people who do not need supplemental oxygen and who are already having corticosteroids for pre-existing or new comorbid conditions, without the need for specific advice in the guideline.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for all-cause mortality within 28 days in both subgroups (adults needing oxygen, and adults not needing oxygen) because of serious imprecision (inconsistent direction of effects for studies of adults needing oxygen and only a single study for adults not needing oxygen). The panel noted that, despite serious imprecision, the pooled effect was statistically significantly in favour of corticosteroids for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of the evidence is moderate for invasive mechanical ventilation or death at 28 days in both subgroups because of serious imprecision (only a single study for both subgroups). The panel noted that, despite serious imprecision, the effect was statistically significantly in favour of dexamethasone for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of evidence is moderate for discharge from hospital in both subgroups because of serious imprecision (inconsistent confidence intervals for studies of adults needing oxygen and only a single study for adults not needing oxygen). However, the panel noted that, for adults with COVID-19 needing oxygen, there was a statistically significant effect in favour of corticosteroids for improving discharge from hospital at 28 days.

Certainty of evidence was moderate for serious adverse events of corticosteroids in adults with COVID-19 needing oxygen. The panel noted that corticosteroids probably have little effect on serious adverse events in this group of people, but were aware of indirect systematic review evidence showing a statistically significant risk of hyperglycaemia among people without COVID-19.

Certainty of evidence was low to moderate for other individual adverse effects, none of which showed statistically significant effects estimates.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences and values. The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who need oxygen, most would choose corticosteroids after shared decision making with healthcare professionals. Dexamethasone was considered to be the preferred corticosteroid treatment because of the larger amount of data supporting its use. The panel agreed that the class effect of corticosteroids would allow for hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

The panel also inferred that, because of the risk of harm, most fully informed people with COVID-19 who do not need supplemental oxygen would not want to have systemic corticosteroids. However, some people may want to consider having this intervention through shared decision making with their healthcare professional.

Resources

No important issues with the recommended alternative

The panel expressed concern over specifying oxygen therapy as a requirement for corticosteroid treatment in a recommendation. They agreed that this may result in inequalities in access to treatments because of certain groups of people not being able to have oxygen therapy, even though their oxygen saturations may indicate that they should. This may also result in supply issues in the event of oxygen shortages. The panel agreed that the emphasis should be on oxygen saturation targets for people who need oxygen supplementation.

The panel noted possible supply issues with corticosteroids in community pharmacies where people are having treatment

outside the hospital setting, such as in residential care. However, they agreed that GP assessment with pulse oximetry and treatment with dexamethasone is realistic in the community setting. The class effect of corticosteroids would allow for suitable alternatives.

Equity

Important issues, or potential issues not investigated

The panel noted limited evidence on the use of corticosteroids in children with COVID-19 but that children should not be excluded from the recommendations. The panel agreed that all age groups should be encompassed with appropriate age-specific advice on dosage.

The panel also noted the lack of evidence on the use of corticosteroids in community settings and the risk of inequitable treatment if limited to people in hospital. The panel were aware of people with COVID-19 needing supplemental oxygen who are having treatment outside the hospital setting and would benefit from corticosteroids. For this reason, the panel agreed that the recommendation should not specify any treatment setting.

See the Resources section for the panel's concern over potential inequality of access to corticosteroids if oxygen therapy is stated as a requirement for corticosteroid treatment, and the need for this to be reflected in the wording of the recommendation.

Acceptability

No important issues with the recommended alternative

The panel considered that acceptability of corticosteroids would be high given the widespread availability, ease of oral ingestion in any setting and established safety profile. They anticipated that, when considering the risks and benefits of treatment through shared decision making, most people with COVID-19 who:

- need supplemental oxygen would choose to have corticosteroids
- do not need supplemental oxygen would choose not to have corticosteroids.

Feasibility

No important issues with the recommended alternative

Although there is no systematically collected evidence about feasibility, the panel noted that the established distribution, supply and use of corticosteroids in clinical practice is an indicator of feasibility.

Rationale

Evidence suggests that, in people with COVID-19 who do not need supplemental oxygen, corticosteroids may increase the risk of needing invasive mechanical ventilation and death at 28 days. The recommendation therefore cautions against using corticosteroids for people not on supplemental oxygen, unless there is another medical indication to do so.

7.2 Casirivimab and imdevimab - for people hospitalised because of COVID-19

Recommended

Updated

Offer a combination of casirivimab and imdevimab to people aged 12 and over hospitalised because of COVID-19 who have no detectable SARS-CoV-2 antibodies (seronegative).

The criteria for accessing casirivimab and imdevimab in the UK, and dosage to be used, are outlined in [NHS England's Interim Clinical Commissioning Policy on casirivimab and imdevimab for patients hospitalised due to COVID-19 \(aged 12 years and above\)](#), published in September 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given casirivimab and imdevimab.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

The panel were presented with evidence from 1 randomised controlled trial (RECOVERY – Horby and Landray 2021). This study looked at people aged 12 and over who were hospitalised because of COVID-19. The treatment was casirivimab and imdevimab (also called Ronapreve, REGEN-COV or REGEN-COV2).

The panel agreed that the evidence from this study showed that there was no marked difference or benefit in the overall population when treated with casirivimab and imdevimab compared to usual care (critical outcomes were mortality, duration of hospitalisation, and progression to invasive mechanical ventilation).

The panel also discussed whether there were significant differences in benefit between and within subgroups of the treatment population. The evidence showed that in people who were seropositive, there was no benefit. However, in people who were seronegative there was a statistically significant reduction in mortality when treated with casirivimab and imdevimab compared to usual care (NNT = around 20). The difference between the results for seronegative and seropositive groups was statistically significant.

The panel discussed the fact that in accordance with protocol, early safety outcomes were not collected throughout the study period. However it was noted that at lower doses side effects are rare. The panel therefore decided that it was likely that the benefit outweighed the risks of treatment based on the available evidence on adverse events.

Based on the evidence, the panel agreed to make a recommendation to offer casirivimab and imdevimab to hospitalised seronegative COVID-19 patients aged 12 and over. The panel discussed whether there was any further evidence to support stratification by different subgroups within the seronegative population, of which there was none. The panel considered subgroups within the seronegative group (for example, age, sex, ethnicity, level of respiratory support, days since symptom onset and use of corticosteroids). Further heterogeneity tests confirmed that no statistically significant differences between subgroups were observed, so the panel agreed that the recommendation could not be further stratified according to subgroups.

The panel acknowledged the need for a serological assay to determine whether someone is seronegative or seropositive. They discussed whether such assays are readily available in the NHS and what the turnaround of these investigations is likely to be. They concluded that they were not aware of any barriers currently to use of serological assays for this purpose in a hospital setting.

The panel also noted the high dosage used in this study population and acknowledged that, at present, there is a lack of evidence about different treatment dosages in people hospitalised with COVID-19. The panel noted that the study did not collect data on whether patients were immunocompromised or vaccinated at baseline and so could not present outcomes for these patient groups. They therefore decided to make a recommendation for research in these areas.

The panel discussed the cost effectiveness of this treatment. However, it was acknowledged that this was out of scope and the panel made recommendations based on the effectiveness and safety evidence.

Certainty of the Evidence

Moderate

The certainty of the evidence was rated as moderate for most outcomes because of serious imprecision. The panel discussed that the issues with imprecision result from few event numbers in some outcomes. Some outcomes within the seronegative subgroup were rated as high certainty.

The panel also noted that safety outcomes were not collected throughout the study period in accordance with study protocol, and early safety data was reported for 30% of the study population. Therefore, the panel concluded that the safety profile of the drugs is not fully understood.

The panel highlighted that the evidence around people who are seronegative was of high certainty and clinical benefit. The panel therefore recommended that this population should be offered the treatment.

Preference and values

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on peoples' preferences and values for treatment with casirivimab and imdevimab. They identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for invasive mechanical ventilation and serious adverse events. It is likely that these outcomes would also be of similar importance to patients.

Resources

Important issues, or potential issues not investigated

The panel discussed the need for prompt testing to determine antibody status and concluded that they were not aware of any barriers currently to use of serological assays for this purpose in a hospital setting. The panel were also aware that the drug could be in short supply. A link to the Interim clinical commissioning policy outlines the eligibility criteria [NHS England's Interim Clinical Commissioning Policy on casirivimab and imdevimab for patients hospitalised due to COVID-19 \(aged 12 years and above\)](#), published in September 2021.

Equity

Important issues, or potential issues not investigated

The panel noted that pregnant and children aged 12 and over were included in the RECOVERY trial, however, no further evidence on the clinical benefit and safety of casirivimab and imdevimab was reported in these participant groups.

No other equity issues were identified.

Acceptability

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about acceptability.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility.

As of 17 September 2021, NHS England outlined certain criteria for accessing casirivimab and imdevimab in the UK [for people hospitalised with COVID-19 \(aged 12 years and above\)](#). The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given casirivimab and imdevimab.

Rationale

Evidence from 1 randomised, controlled trial in people aged 12 years and over who were hospitalised because of COVID-19 and receiving casirivimab and imdevimab suggests possible benefit of this treatment when compared to usual care for seronegative people. The results from this trial suggest that casirivimab and imdevimab reduced mortality for seronegative people who were hospitalised with COVID-19 when compared to usual care.

The panel decided that the benefits outweighed the risks of treatment based on the available evidence on adverse events in the

study and known side effects from the Summary of Product Characteristics (SmPC). As such, this treatment was recommended for seronegative people aged 12 years and over with COVID-19 infection.

Clinical Question/ PICO

Population: People with COVID-19 (Hospitalised)
Intervention: Casirivimab + Imdevimab
Comparator: Usual Care

Summary

What is the evidence informing this recommendation?

Evidence comes from 1 randomised controlled trial with 9,785 participants included. Results from one study, the RECOVERY trial, were reported in Horby and Landray 2021.

The study compared a single dose of intravenous casirivimab (4g) imdevimab (4g) (n=4,839) with usual care (n=4,946). Usual care treatment varied but included corticosteroids (94%), aspirin (28%), remdesivir (25%), colchicine (23%) and tocilizumab or sarilumab (16%).

Study characteristics

The study population was derived from 127 sites in the United Kingdom. Participants aged >12 years, who were hospitalised with COVID-19 were recruited between 18 September 2020 and 22 May 2021. COVID-19 diagnosis was confirmed by a positive polymerase chain reaction (PCR) test. The mean age in the study was around 62 years and 63% of participants were male. Approximately 77% of participants were White, 13% Black, Asian, and minority ethnic groups, and the remainder of unknown ethnicity. It was a median of 9 [IQR 6-12] days since symptom onset, and median 2 (IQR 1-3) days since admission to hospital. Approximately 7% of participants received no oxygen, 62% simple oxygen, 26% non-invasive ventilation and 6% invasive mechanical ventilation. Approximately 54% of participants were positive for SARS-CoV-2 antibody, 32% negative and in 14% these data were missing. Approximately 53% of participants reported comorbidity (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus (HIV), severe liver disease requiring ongoing specialist care, or severe kidney impairment with estimated glomerular filtration rate <30 mL/min per 1.73 m²). Approximately 94% of participants in both groups were treated with corticosteroids 25% with remdesivir and 16% with tocilizumab or sarilumab. Lastly, pregnant or breastfeeding women were eligible for inclusion.

Exclusion criteria varied, but patients who received intravenous immunoglobulin treatment during the current admission and children weighing less than 40kg and were younger than 12 years old were excluded.

Outcomes were assessed within 28 days after randomisation.

What are the main results?

Mortality – All patients

Moderate quality evidence from 1 study found no statistically significant reduction in overall mortality at 28 days in all participants hospitalised with COVID-19, who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 0.94, CI 95% 0.87 - 1.02; 9,785 people in 1 study].

Mortality - Seropositive

Moderate quality evidence from 1 study found no statistically significant reduction in mortality at 28 days in seropositive people, hospitalised with COVID-19, who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 1.07, CI 95% 0.94 - 1.22; 5,272 people in 1 study].

Mortality - Seronegative

High quality evidence from 1 study found a statistically significant reduction in mortality at 28 days in seronegative people, hospitalised with COVID-19 who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 0.82, CI 95% 0.73 - 0.92; 3,153 people in 1 study].

Invasive mechanical ventilation - All patients

Moderate quality evidence from 1 study found no statistically significant difference in progression to invasive mechanical ventilation at 28 days in all study participants who were hospitalised with COVID-19, and who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 1.00, CI 95% 0.89 - 1.13; 9,198 people in 1 study].

Invasive mechanical ventilation - Seropositive

High quality evidence from 1 study found a statistically significant increase in progression to invasive mechanical ventilation at 28 days in people who were seropositive and treated with casirivimab and imdevimab compared to usual care. [Relative risk 1.17, CI 95% 1.01 - 1.36; 4,989 people in 1 study].

Invasive mechanical ventilation - Seronegative

High quality evidence from 1 study found a statistically significant reduction in progression to invasive mechanical ventilation at 28 days in people who were seropositive and treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.76, CI 95% 0.66 - 0.88; 3,083 people in 1 study].

Non-invasive ventilation - All patients

High quality evidence from 1 study found no statistically significant difference in progression to non-invasive ventilation at 28 days in all study participants who were treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.94, CI 95% 0.84 - 1.05; 6,637 people in 1 study].

Non-invasive ventilation - Seronegative

High quality evidence from 1 study found a statistically significant reduction in progression to non-invasive ventilation at 28 days in people who were seronegative and treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.80, CI 95% 0.67 - 0.96; 2,410 people in 1 study].

Adverse Events - Severe allergic reaction

Low quality evidence from 1 study found no statistically significant difference in severe allergic reactions in people who were hospitalised with COVID-19, and who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 3.83, CI 95% 0.43 - 34.20; 3,506 people in 1 study].

Duration of hospitalisation - All patients

Low quality evidence from 1 study is uncertain about whether treatment with casirivimab and imdevimab in all patients has an effect on the duration of hospitalisation compared to usual care. [Median 10 (IQR: 22) days and Median 10 (IQR: 23) days; 9,785 people in 1 study].

Duration of hospitalisation - Seronegative

Low quality evidence from 1 study is uncertain about whether treatment with casirivimab and imdevimab in the seronegative subgroup has an effect on the duration of hospitalisation compared to usual care. [Median 13 (IQR: 21) days and Median 17 (IQR: 21) days; 3,153 people in 1 study].

Our confidence in the results

Evidence includes one open-label RCT with 9,785 participants (4,839 in treatment arm and 4,946 in control arm). While there are clear reasons for this, it is unlikely to affect the incidence of objective outcomes such as death, invasive ventilation and duration of hospitalisation. The included study was a pre-print and as such was not peer-reviewed.

The strengths of this trial included: appropriate randomisation with allocation concealment, similarity between baseline characteristics in both treatment and control groups and lastly the study population was large and included broad eligibility criteria and the study population was large. Overall it was rated as low risk of bias in all outcomes and domains.

The limitations of the study include the fact that the dose of casirivimab (4g) and imdevimab (4g) used was high compared to similar studies conducted in community settings. Moreover, data on factors such virological load, physiological outcomes, number of patients with clinical deterioration or development of long-term effects of COVID-19 were not collected.

Further subgroup analyses for outcomes within the seronegative population were conducted to identify evidence of marked treatment benefit in specific groups. However, there were no statistically significant differences within these subgroups.

Certainty of the evidence is low for median duration of hospitalisation in all patients and seronegative subgroup, as well as severe allergic reactions, due to very serious imprecision (confidence interval included the line of no effect and low numbers of participants).

Certainty of the evidence is moderate for mortality in all patients in the study and mortality in the seropositive subgroup, progression to invasive mechanical ventilation in all patients and the seropositive subgroup, due to serious imprecision (confidence intervals included the line of no effect).

Certainty of the evidence is high for mortality in people who were seronegative, as well as progression to invasive mechanical ventilation for the seropositive and seronegative subgroups, progression to non-invasive mechanical ventilation in all patients and in the seronegative subgroup.

Outcome Timeframe	Study results and measurements	Comparator Usual Care	Intervention Casirivimab + Imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality [All patients] Within 28 days of randomisation 9 Critical	Relative risk 0.94 (CI 95% 0.87 – 1.02) Based on data from 9,785 patients in 1 studies. ¹ (Randomized controlled)	207 per 1000 Difference:	195 per 1000 12 fewer per 1000 (CI 95% 27 fewer – 4 more)	Moderate Due to serious imprecision ²	One study found no statistically significant difference in mortality for all participants included in the study who were hospitalised with COVID-19 infection and treated with casirivimab and imdevimab compared to usual care.

Outcome Timeframe	Study results and measurements	Comparator Usual Care	Intervention Casirivimab + Imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality [Seropositive] Within 28 days of randomisation 9 Critical	Relative risk 1.07 (CI 95% 0.94 – 1.22) Based on data from 5,272 patients in 1 studies. ³ (Randomized controlled)	145 per 1000 Difference:	155 per 1000 10 more per 1000 (CI 95% 9 fewer – 32 more)	Moderate Due to serious imprecision ⁴	One study found no statistically significant difference in mortality in people who were seropositive for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Mortality [Seronegative] Within 28 days of randomisation 9 Critical	Relative risk 0.82 (CI 95% 0.73 – 0.92) Based on data from 3,153 patients in 1 studies. ⁵ (Randomized controlled)	297 per 1000 Difference:	244 per 1000 53 fewer per 1000 (CI 95% 80 fewer – 24 fewer)	High	One study found a statistically significant reduction in mortality for people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [All patients] Within 28 days of randomisation 9 Critical	Relative risk 1 (CI 95% 0.89 – 1.13) Based on data from 9,198 patients in 1 studies. ⁶ (Randomized controlled)	105 per 1000 Difference:	105 per 1000 0 fewer per 1000 (CI 95% 12 fewer – 14 more)	Moderate Due to serious imprecision ⁷	One study found no statistically significant difference in progression to invasive mechanical ventilation for overall study participants who were not on invasive mechanical ventilation at randomisation and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [Seropositive] Within 28 days of randomisation 9 Critical	Odds Ratio 1.17 (CI 95% 1.01 – 1.36) Based on data from 4,989 patients in 1 studies. ⁸ (Randomized controlled)	163 per 1000 Difference:	185 per 1000 23 more per 1000 (CI 95% 1 more – 46 more)	High	One study found a statistically significant increase in the progression to invasive mechanical ventilation among people who were seropositive for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [Seronegative] Within 28 days of randomisation 9 Critical	Odds Ratio 0.76 (CI 95% 0.66 – 0.88) Based on data from 3,083 patients in 1 studies. ⁹ (Randomized controlled)	365 per 1000 Difference:	304 per 1000 61 fewer per 1000 (CI 95% 90 fewer – 29 fewer)	High	One study found a statistically significant reduction in progression to invasive mechanical ventilation in people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.

Outcome Timeframe	Study results and measurements	Comparator Usual Care	Intervention Casirivimab + Imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Non-invasive ventilation [All patients] Within 28 days of randomisation 6 Important	Odds Ratio 0.94 (CI 95% 0.84 – 1.05) Based on data from 6,637 patients in 1 studies. ¹⁰ (Randomized controlled)	230 per 1000 Difference:	219 per 1000 11 fewer per 1000 (CI 95% 29 fewer – 9 more)	High	One study found no statistically significant difference in progression to non-invasive ventilation in all hospitalised patients who were treated with casirivimab and imdevimab compared to usual care.
Non-invasive ventilation [Seronegative] Within 28 days of randomisation 6 Important	Odds Ratio 0.8 (CI 95% 0.67 – 0.96) Based on data from 2,410 patients in 1 studies. ¹¹ (Randomized controlled)	315 per 1000 Difference:	268 per 1000 46 fewer per 1000 (CI 95% 79 fewer – 9 fewer)	High	One study found a statistically significant reduction in progression to non-invasive mechanical ventilation in people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Adverse events [Severe allergic reaction] 72 hours 6 Important	Relative risk 3.83 (CI 95% 0.43 – 34.2) Based on data from 3,506 patients in 1 studies. ¹² (Randomized controlled)	1 per 1000 Difference:	4 per 1000 3 more per 1000 (CI 95% 1 fewer – 33 more)	Low Due to very serious imprecision ¹³	One study found no statistically significant difference in severe allergic reactions in hospitalised people treated with casirivimab+imdevimab compared to usual care.
Median duration of hospitalisation [All patients] Days 6 Important	Lower better Based on data from: 9,785 patients in 1 studies. (Randomized controlled)	10 (Median)	10 (Median) CI 95%	Low Due to very serious imprecision ¹⁴	It is uncertain whether treatment with casirivimab and imdevimab has an effect on the median duration of hospitalisation in all patients included in the study compared to usual care.
Median duration of hospitalisation [Seronegative] Days 6 Important	Lower better Based on data from: 3,153 patients in 1 studies. (Randomized controlled)	17 (Median)	13 (Median) CI 95%	Low Due to very serious imprecision ¹⁵	It is uncertain whether treatment with casirivimab and imdevimab has an effect on the median duration of hospitalisation in all patients included in the study compared to usual care.

1. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI cross the line of no effect. **Publication bias: no serious.**
3. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included the line of no effect. **Publication bias: no serious.**
5. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included the line of no effect. **Publication bias: no serious.**
8. Systematic review [100] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
9. Systematic review [100] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [103] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [103] with included studies: Horby 2021, Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** CI included the line of no effect and wide confidence intervals due to small number of events. **Publication bias: no serious.**
14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Outcome is not comparable. **Publication bias: no serious.**
15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Outcome is not comparable. **Publication bias: no serious.**

References

87. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.
100. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.
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102. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.
103. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

Not recommended

Updated

Do not offer a combination of casirivimab and imdevimab to people aged 12 and over hospitalised because of COVID-19:

- who have detectable SARS-CoV-2 antibodies (seropositive), or
- whose serostatus is unknown.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel were presented with evidence from 1 randomised controlled trial (RECOVERY – Horby and Landray 2021). This study looked at people aged 12 and over who were hospitalised because of COVID-19. The treatment was casirivimab and imdevimab (also called Ronapreve, REGEN-COV or REGEN-COV2).

The panel agreed that the results from this study showed no marked difference or benefit in the overall population when

treated with casirivimab and imdevimab compared to usual care (critical outcomes were: mortality, duration of hospitalisation, progression to invasive mechanical ventilation). The panel also noted the high dosage used in this study population and that at present, there is a lack of evidence about different treatment dosages in people hospitalised with COVID-19.

The panel noted that the proportion of seropositive people hospitalised with COVID-19 is expected to be higher because of the high numbers of the population vaccinated against SARS-CoV-2 and possibly because of previous infection with COVID-19. The panel noted that the study did not account for immunocompromised patients, patients who are vaccinated and patients with unknown serostatus and the outcomes within these specific patient groups. They therefore decided to make a recommendation for research in these areas.

The panel discussed whether there were significant differences in benefit between and within subgroups of the treatment population. The study reported serostatus of subgroups, and the evidence from the study showed that in people who were seropositive or of unknown serostatus there was no benefit in treatment with casirivimab and imdevimab when compared to usual care.

The panel discussed the fact that early safety outcomes were not collected throughout the full study period, in accordance with the study protocol. However, it was noted that at lower doses than those used in the RECOVERY trial, side effects are rare. However, the panel agreed that in seropositive or unknown serostatus groups risk of adverse events could not be determined based on the data reported in the RECOVERY trial.

Certainty of the Evidence

Moderate

The certainty of the evidence was rated as moderate for most outcomes because of serious imprecision. The panel discussed that these issues with imprecision result from few event numbers in some outcomes.

The panel also noted that safety outcomes were not collected throughout the study period in accordance with study protocol. Early safety data was reported for 30% of the study population and so the safety profile of the drugs is not fully understood.

The panel discussed that the evidence around people who were seropositive or of unknown serostatus was less certain but indicated a potential harm of the treatment. The panel therefore recommended that they should not be offered the treatment.

Preference and values

We expect few to want the intervention

The panel were not aware of any systematically collected data on peoples' preferences and values for treatment with casirivimab and imdevimab. They identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for invasive mechanical ventilation and serious adverse events. It is likely that these outcomes would also be of similar importance to patients.

The panel inferred that, in view of the evidence provided, most people who are seropositive or with an unknown serostatus for SARS-CoV-2 antibodies would not choose treatment with casirivimab and imdevimab.

Resources

Important issues, or potential issues not investigated

The panel discussed the need for prompt testing to determine antibody status and concluded that they were not aware of any barriers currently to use of serological assays for this purpose in a hospital setting. The panel were also aware that the drug could be in short supply. A link to the Interim clinical commissioning policy outlines the eligibility criteria [NHS England's Interim Clinical Commissioning Policy on casirivimab and imdevimab for patients hospitalised due to COVID-19 \(aged 12 years and above\)](#), published in September 2021.

Equity

Important issues, or potential issues not investigated

The panel noted that pregnant and children aged 12 and over were included in the RECOVERY trial, however, no further evidence on the clinical benefit and safety of casirivimab and imdevimab was reported in these participant groups.

No other equity issues were identified.

Acceptability

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about acceptability.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility.

As of 17 September 2021, NHS England outlined certain criteria for accessing casirivimab and imdevimab in the UK [for people hospitalised with COVID-19 \(aged 12 years and above\)](#). The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given casirivimab and imdevimab.

Rationale

Evidence from 1 randomised, controlled trial did not suggest benefit from treatment with casirivimab and imdevimab for people aged over 12 years who are hospitalised because of COVID-19 and who are seropositive or of an unknown serostatus. The results showed that, compared with usual care, casirivimab and imdevimab did not reduce incidence of mortality, duration of hospitalisation, progression to invasive mechanical ventilation or adverse events incidence in people who are seropositive or of an unknown serostatus.

The panel agreed not to recommend treatment with casirivimab and imdevimab for people who are seropositive or of an unknown serostatus.

Clinical Question/ PICO

Population: People with COVID-19 (Hospitalised)
Intervention: Casirivimab + Imdevimab
Comparator: Usual Care

Summary**What is the evidence informing this recommendation?**

Evidence comes from 1 randomised controlled trial with 9,785 participants included. Results from one study, the RECOVERY trial, were reported in Horby and Landray 2021.

The study compared a single dose of intravenous casirivimab (4g) imdevimab (4g) (n=4,839) with usual care (n=4,946). Usual care treatment varied but included corticosteroids (94%), aspirin (28%), remdesivir (25%), colchicine (23%) and tocilizumab or sarilumab (16%).

Study characteristics

The study population was derived from 127 sites in the United Kingdom. Participants aged >12 years, who were hospitalised with COVID-19 were recruited between 18 September 2020 and 22 May 2021. COVID-19 diagnosis was confirmed by a positive polymerase chain reaction (PCR) test. The mean age in the study was around 62 years and 63% of participants were male. Approximately 77% of participants were White, 13% Black, Asian, and minority ethnic groups, and the remainder of unknown ethnicity. It was a median of 9 [IQR 6-12] days since symptom onset, and median 2 (IQR 1-3) days since admission to hospital. Approximately 7% of participants received no oxygen, 62% simple oxygen,

26% non-invasive ventilation and 6% invasive mechanical ventilation. Approximately 54% of participants were positive for SARS-CoV-2 antibody, 32% negative and in 14% these data were missing. Approximately 53% of participants reported comorbidity (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus (HIV), severe liver disease requiring ongoing specialist care, or severe kidney impairment with estimated glomerular filtration rate <30 mL/min per 1.73 m²). Approximately 94% of participants in both groups were treated with corticosteroids 25% with remdesivir and 16% with tocilizumab or sarilumab. Lastly, pregnant or breastfeeding women were eligible for inclusion.

Exclusion criteria varied, but patients who received intravenous immunoglobulin treatment during the current admission and children weighing less than 40kg and were younger than 12 years old were excluded.

Outcomes were assessed within 28 days after randomisation.

What are the main results?

Mortality – All patients

Moderate quality evidence from 1 study found no statistically significant reduction in overall mortality at 28 days in all participants hospitalised with COVID-19, who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 0.94, CI 95% 0.87 - 1.02; 9,785 people in 1 study].

Mortality - Seropositive

Moderate quality evidence from 1 study found no statistically significant reduction in mortality at 28 days in seropositive people, hospitalised with COVID-19, who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 1.07, CI 95% 0.94 - 1.22; 5,272 people in 1 study].

Mortality - Seronegative

High quality evidence from 1 study found a statistically significant reduction in mortality at 28 days in seronegative people, hospitalised with COVID-19 who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 0.82, CI 95% 0.73 - 0.92; 3,153 people in 1 study].

Invasive mechanical ventilation - All patients

Moderate quality evidence from 1 study found no statistically significant difference in progression to invasive mechanical ventilation at 28 days in all study participants who were hospitalised with COVID-19, and who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 1.00, CI 95% 0.89 - 1.13; 9,198 people in 1 study].

Invasive mechanical ventilation - Seropositive

High quality evidence from 1 study found a statistically significant increase in progression to invasive mechanical ventilation at 28 days in people who were seropositive and treated with casirivimab and imdevimab compared to usual care. [Relative risk 1.17, CI 95% 1.01 - 1.36; 4,989 people in 1 study].

Invasive mechanical ventilation - Seronegative

High quality evidence from 1 study found a statistically significant reduction in progression to invasive mechanical ventilation at 28 days in people who were seropositive and treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.76, CI 95% 0.66 - 0.88; 3,083 people in 1 study].

Non-invasive ventilation - All patients

High quality evidence from 1 study found no statistically significant difference in progression to non-invasive ventilation at 28 days in all study participants who were treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.94, CI 95% 0.84 - 1.05; 6,637 people in 1 study].

Non-invasive ventilation - Seronegative

High quality evidence from 1 study found a statistically significant reduction in progression to non-invasive ventilation at 28 days in people who were seronegative and treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.80, CI 95% 0.67 - 0.96; 2,410 people in 1 study].

Adverse Events - Severe allergic reaction

Low quality evidence from 1 study found no statistically significant difference in severe allergic reactions in people who were hospitalised with COVID-19, and who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 3.83, CI 95% 0.43 - 34.20; 3,506 people in 1 study].

Duration of hospitalisation - All patients

Low quality evidence from 1 study is uncertain about whether treatment with casirivimab and imdevimab in all patients has an effect on the duration of hospitalisation compared to usual care. [Median 10 (IQR: 22) days and Median 10 (IQR: 23) days; 9,785 people in 1 study].

Duration of hospitalisation - Seronegative

Low quality evidence from 1 study is uncertain about whether treatment with casirivimab and imdevimab in the seronegative subgroup has an effect on the duration of hospitalisation compared to usual care. [Median 13 (IQR: 21) days and Median 17 (IQR: 21) days; 3,153 people in 1 study].

Our confidence in the results

Evidence includes one open-label RCT with 9,785 participants (4,839 in treatment arm and 4,946 in control arm). While there are clear reasons for this, it is unlikely to affect the incidence of objective outcomes such as death, invasive ventilation and duration of hospitalisation. The included study was a pre-print and as such was not peer-reviewed.

The strengths of this trial included: appropriate randomisation with allocation concealment, similarity between baseline characteristics in both treatment and control groups and lastly the study population was large and included broad eligibility criteria and the study population was large. Overall it was rated as low risk of bias in all outcomes and domains.

The limitations of the study include the fact that the dose of casirivimab (4g) and imdevimab (4g) used was high compared to similar studies conducted in community settings. Moreover, data on factors such virological load, physiological outcomes, number of patients with clinical deterioration or development of long-term effects of COVID-19 were not collected.

Further subgroup analyses for outcomes within the seronegative population were conducted to identify evidence of marked treatment benefit in specific groups. However, there were no statistically significant differences within these subgroups.

Certainty of the evidence is low for median duration of hospitalisation in all patients and seronegative subgroup, as well as severe allergic reactions, due to very serious imprecision (confidence interval included the line of no effect and low

numbers of participants).

Certainty of the evidence is moderate for mortality in all patients in the study and mortality in the seropositive subgroup, progression to invasive mechanical ventilation in all patients and the seropositive subgroup, due to serious imprecision (confidence intervals included the line of no effect).

Certainty of the evidence is high for mortality in people who were seronegative, as well as progression to invasive mechanical ventilation for the seropositive and seronegative subgroups, progression to non-invasive mechanical ventilation in all patients and in the seronegative subgroup.

Outcome Timeframe	Study results and measurements	Comparator Usual Care	Intervention Casirivimab + Imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality [All patients] Within 28 days of randomisation 9 Critical	Relative risk 0.94 (CI 95% 0.87 – 1.02) Based on data from 9,785 patients in 1 studies. ¹ (Randomized controlled)	207 per 1000 Difference:	195 per 1000 12 fewer per 1000 (CI 95% 27 fewer – 4 more)	Moderate Due to serious imprecision ²	One study found no statistically significant difference in mortality for all participants included in the study who were hospitalised with COVID-19 infection and treated with casirivimab and imdevimab compared to usual care.
Mortality [Seropositive] Within 28 days of randomisation 9 Critical	Relative risk 1.07 (CI 95% 0.94 – 1.22) Based on data from 5,272 patients in 1 studies. ³ (Randomized controlled)	145 per 1000 Difference:	155 per 1000 10 more per 1000 (CI 95% 9 fewer – 32 more)	Moderate Due to serious imprecision ⁴	One study found no statistically significant difference in mortality in people who were seropositive for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Mortality [Seronegative] Within 28 days of randomisation 9 Critical	Relative risk 0.82 (CI 95% 0.73 – 0.92) Based on data from 3,153 patients in 1 studies. ⁵ (Randomized controlled)	297 per 1000 Difference:	244 per 1000 53 fewer per 1000 (CI 95% 80 fewer – 24 fewer)	High	One study found a statistically significant reduction in mortality for people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [All patients] Within 28 days of randomisation	Relative risk 1 (CI 95% 0.89 – 1.13) Based on data from 9,198 patients in 1 studies. ⁶ (Randomized controlled)	105 per 1000 Difference:	105 per 1000 0 fewer per 1000 (CI 95% 12 fewer – 14 more)	Moderate Due to serious imprecision ⁷	One study found no statistically significant difference in progression to invasive mechanical ventilation for overall study participants who were not on invasive

Outcome Timeframe	Study results and measurements	Comparator Usual Care	Intervention Casirivimab + Imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
9 Critical					mechanical ventilation at randomisation and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [Seropositive] Within 28 days of randomisation 9 Critical	Odds Ratio 1.17 (CI 95% 1.01 – 1.36) Based on data from 4,989 patients in 1 studies. ⁸ (Randomized controlled)	163 per 1000 Difference:	185 per 1000 23 more per 1000 (CI 95% 1 more – 46 more)	High	One study found a statistically significant increase in the progression to invasive mechanical ventilation among people who were seropositive for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [Seronegative] Within 28 days of randomisation 9 Critical	Odds Ratio 0.76 (CI 95% 0.66 – 0.88) Based on data from 3,083 patients in 1 studies. ⁹ (Randomized controlled)	365 per 1000 Difference:	304 per 1000 61 fewer per 1000 (CI 95% 90 fewer – 29 fewer)	High	One study found a statistically significant reduction in progression to invasive mechanical ventilation in people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Non-invasive ventilation [All patients] Within 28 days of randomisation 6 Important	Odds Ratio 0.94 (CI 95% 0.84 – 1.05) Based on data from 6,637 patients in 1 studies. ¹⁰ (Randomized controlled)	230 per 1000 Difference:	219 per 1000 11 fewer per 1000 (CI 95% 29 fewer – 9 more)	High	One study found no statistically significant difference in progression to non-invasive ventilation in all hospitalised patients who were treated with casirivimab and imdevimab compared to usual care.
Non-invasive ventilation [Seronegative] Within 28 days of randomisation 6 Important	Odds Ratio 0.8 (CI 95% 0.67 – 0.96) Based on data from 2,410 patients in 1 studies. ¹¹ (Randomized controlled)	315 per 1000 Difference:	268 per 1000 46 fewer per 1000 (CI 95% 79 fewer – 9 fewer)	High	One study found a statistically significant reduction in progression to non-invasive mechanical ventilation in people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Adverse events [Severe allergic reaction] 72 hours	Relative risk 3.83 (CI 95% 0.43 – 34.2) Based on data from 3,506 patients in 1	1 per 1000 Difference:	4 per 1000 3 more per 1000	Low Due to very serious imprecision ¹³	One study found no statistically significant difference in severe allergic reactions in

Outcome Timeframe	Study results and measurements	Comparator Usual Care	Intervention Casirivimab + Imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important	studies. ¹² (Randomized controlled)		(CI 95% 1 fewer — 33 more)		hospitalised people treated with casirivimab+imdevimab compared to usual care.
Median duration of hospitalisation [All patients] Days 6 Important	Lower better Based on data from: 9,785 patients in 1 studies. (Randomized controlled)	10 (Median)	10 (Median) CI 95%	Low Due to very serious imprecision ¹⁴	It is uncertain whether treatment with casirivimab and imdevimab has an effect on the median duration of hospitalisation in all patients included in the study compared to usual care.
Median duration of hospitalisation [Seronegative] Days 6 Important	Lower better Based on data from: 3,153 patients in 1 studies. (Randomized controlled)	17 (Median)	13 (Median) CI 95%	Low Due to very serious imprecision ¹⁵	It is uncertain whether treatment with casirivimab and imdevimab has an effect on the median duration of hospitalisation in all patients included in the study compared to usual care.

1. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI cross the line of no effect. **Publication bias: no serious.**
3. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included the line of no effect. **Publication bias: no serious.**
5. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included the line of no effect. **Publication bias: no serious.**
8. Systematic review [100] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
9. Systematic review [100] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [103] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [103] with included studies: Horby 2021, Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** CI included the line of no effect and wide confidence intervals due to small number of events. **Publication bias: no serious.**
14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Outcome is not comparable. **Publication bias: no serious.**
15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Outcome is not comparable. **Publication bias: no serious.**

References

87. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.
100. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.
101. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.
102. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.
103. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

7.3 Remdesivir

Info Box

Definitions

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the [Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'](#).

Low-flow oxygen supplementation: oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min.

Conditional recommendation

Consider remdesivir for up to 5 days for COVID-19 pneumonia in adults, and young people 12 years and over weighing 40 kg or more, in hospital and needing low-flow supplemental oxygen.

The criteria for accessing remdesivir in the UK are outlined in [NHS England's Interim Clinical Commissioning Policy on remdesivir for patients hospitalised with COVID-19 \(adults and children 12 years and older\)](#), which was updated in June 2021 to include eligibility criteria for remdesivir in people who are significantly immunocompromised.

For remdesivir use in pregnancy, follow the [Royal College of Obstetrics and Gynaecology guidance on coronavirus \(COVID-19\) infection and pregnancy](#).

The marketing authorisation for remdesivir for COVID-19 does not include children under 12 years or weighing less than 40 kg.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel noted the opposing directions of effect between people receiving high-flow oxygen, non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV), which showed a trend towards higher all-cause mortality, and people receiving low-flow oxygen supplementation or no oxygen, which showed a trend towards lower all-cause mortality. The duration and severity of disease was considered the explanation. The panel were presented with a clinical rationale for antiviral treatment, which supports the thinking that antivirals are expected to be most effective early in the disease course, when viral replication is a driver of disease. Antivirals are less likely to be effective in the later stages in the disease course when it enters the hyperinflammatory phase. This phase is often associated with the need for more respiratory support.

Although not always described in the evidence, the panel considered that continuous positive airway pressure (CPAP) was included as a type of NIV.

Evidence from randomised controlled trials of remdesivir compared with standard care show that remdesivir has an acceptable safety profile and may reduce the incidence of serious adverse events.

Based on the results of 2 studies that compared 10-day with 5-day courses of remdesivir, it is unclear which of these regimens provides the optimal treatment duration. The current evidence does not suggest any greater benefit for a 10-day duration but suggests an increased risk of harm. The panel also acknowledged that, if disease progression resulted in the need for more respiratory support while using remdesivir, there may be no benefit in completing the full course. For these reasons, along with resource impact considerations (see also Resources), the panel agreed to recommend remdesivir for up to 5 days.

The panel noted the unclear additive benefit of remdesivir when used with dexamethasone, particularly because the 2 main trials, SOLIDARITY and ACTT-1, were done before the routine use of dexamethasone.

The panel also reviewed academic-in-confidence data from an observational study but did not consider this to have any effect on the recommendations.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for death in both subgroups (people who need low-flow oxygen supplementation or no oxygen, and people who need high-flow oxygen supplementation, NIV or IMV), all because of serious imprecision (wide confidence intervals). The panel noted difficulties in disaggregating data on different modalities of respiratory support to inform subgroup analysis, with some trials covering both NIV and IMV. However, the panel agreed that subgroup data should be distinguished between high-flow oxygen, NIV or IMV and low-flow oxygen modalities in the pooled meta-analysis of included studies. The panel noted that, despite serious imprecision, the direction of effect was consistently in favour of remdesivir across studies for people receiving low-flow oxygen or no oxygen. They agreed that a 'consider' recommendation for people on low-flow supplementary oxygen and not on high-flow oxygen, NIV or IMV would allow clinical discretion in making individualised treatment decisions, and would reflect the level of uncertainty in the evidence.

Certainty is also moderate for the outcomes of number of people needing ventilation and discharge from hospital (because of reliance on a single study), and serious adverse events, time to recovery and time to improvement (because of non-blinding of people in the trial and personnel).

Certainty of the evidence is low for respiratory failure or acute respiratory distress syndrome (because of inconsistency in direction of effect and wide confidence intervals), number of people needing IMV or extracorporeal membrane oxygenation (because of non-blinding of people in the trial and personnel, and reliance on a single study), clinical recovery and adverse events (because of non-blinding of people in the trial and personnel, and inconsistency in direction of effect) and stopping treatment because of adverse events (because of non-blinding of people in the trial and personnel, and wide confidence intervals). Certainty of the evidence is very low for septic shock (because of non-blinding of people in the trial and personnel, inconsistency in direction of effect and wide confidence intervals).

Preference and values

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on peoples' preferences and values. They identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for IMV and serious adverse events. It is likely that these outcomes would also be of similar importance to patients. In addition, other outcomes including less serious adverse events, discharge from hospital, duration of hospital stay and longer-term outcomes such as functional independence are likely to be of particular importance to patients. These outcomes were not as commonly reported in studies.

The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who need low-flow oxygen supplementation, most would choose remdesivir.

Resources

Important issues, or potential issues not investigated

Cost effectiveness was not assessed as part of the evidence review.

The panel raised concerns about opportunity costs where remdesivir is being used in critical care, and the importance of not diverting resources away from best supportive care. The panel noted the value of targeting treatment to optimise use of resources. The panel also noted the lack of evidence showing any benefit of a 10-day over a 5-day regimen, a direction of effect indicating potential harms of the 10-day duration and the resource impact for a longer treatment duration. See also the benefits and harms section.

Equity

Important issues, or potential issues not investigated

The panel noted an absence of evidence from randomised trials on remdesivir use in children. However, it was considered unlikely that most children would benefit from this intervention because most children will recover without the need for it. It is also not licensed for use in children under 12 years. Children over 12 years, weighing 40 kg or more, and with adult phenotype disease should have treatment based on the same indications as those used for adults, in particular, if there is progressive respiratory deterioration. Children with comorbidities with significant lung disease may have benefit from treatment with remdesivir, but their treatment should be discussed on a case-by-case basis with the paediatric infectious diseases team.

The panel also noted the absence of evidence on the use of remdesivir in community settings. However, they considered it unlikely that it would be used outside the hospital setting because the criteria for accessing remdesivir in the UK currently stipulate hospitalisation with COVID-19.

No evidence for using remdesivir in pregnancy was identified. The marketing authorisation confirms the lack of evidence, and notes that remdesivir should be avoided in pregnancy unless 'the clinical condition of the women requires treatment with it'. Any decisions to use remdesivir in someone who is pregnant should involve them and a multidisciplinary team, if possible.

No other equity issues were identified.

Acceptability

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about acceptability. A potential deterring factor to acceptability could be that the certainty of current evidence is only moderate. However, the panel noted the consistent direction of effect in favour of remdesivir for those on lower levels of respiratory support.

It is anticipated that, when considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia and need low-flow oxygen supplementation would choose to have remdesivir.

Feasibility

Important issues, or potential issues not investigated

Although there is no systematically collected evidence about feasibility, the panel noted that current widespread use of remdesivir in clinical practice is an indicator of feasibility.

Rationale

There is limited evidence suggesting that remdesivir probably reduces the risk of death in people in hospital with COVID-19 pneumonia needing low-flow oxygen supplementation. This is likely because it is being given early in the disease course (that is, before the need for high-flow oxygen supplementation, non-invasive ventilation or invasive mechanical ventilation) when viral replication is a driver of disease.

The evidence for remdesivir in children and young people is limited. However, the panel were aware that the marketing authorisation for remdesivir for COVID-19 includes young people aged 12 years and over weighing 40 kg or more.

The evidence does not suggest any greater benefit with a 10-day course of remdesivir compared with a 5-day course, but

suggests an increased risk of harm. There may also be no benefit in completing the full course of remdesivir if there is progression to high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation during treatment. The panel also acknowledged that using remdesivir for longer would have greater resource implications.

Clinical Question/ PICO

Population: People with COVID-19
Intervention: Remdesivir
Comparator: Placebo or standard care

Summary

Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised people who require no or low-flow oxygen.

Compared with standard care, remdesivir probably increases death at day 28 in people who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care.

What is the evidence informing this recommendation?

Evidence comes from 4 randomised controlled trials that compared remdesivir with standard care in 7333 adults hospitalised with COVID-19 (Beigel 2020, Pan 2020, Spinner 2020, Wang 2020). The majority of evidence is from the WHO SOLIDARITY and ACTT-1 trials, which randomised 5451 and 1062 patients with moderate to critical COVID-19 (Pan 2020, Beigel 2020).

The evidence for mortality was divided into 2 analyses based on the level of respiratory support required. This is because it is expected that antivirals will most likely be more effective in the early stages of disease progression. The levels of respiratory support have been used as a proxy to measure disease progression in the trials. Low levels of respiratory support were considered to be no oxygen supplementation or low-flow oxygen supplementation. Higher levels of respiratory support included, high-flow oxygen supplementation, non-invasive ventilation (NIV) [such as Bilevel Positive Airway Pressure (BiPAP) and Continuous Positive Airway Pressure (CPAP)] and invasive ventilation.

The ACTT-1 trial was conducted very early in the pandemic and may not be reflective of current standard care practices. A sensitivity analysis was conducted for key outcomes.

Study characteristics

Mean or median age ranged from 56 to 66 years and women comprised 32 to 44% of patients across the studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more. There was variability in levels of respiratory support among patients included in the trials (see table).

Levels of respiratory support in trial participants

Level of respiratory support	Beigel 2020 (n=1062)	Wang 2020 (n=236)	Spinner 2020 (n=584)	Pan 2020 (n=5451)
No oxygen or low-flow oxygen supplementation	573 (54%)	197 (83%)	584 (100%)	4964 (91%)
High-flow oxygen supplementation or NIV	193 (18%)	39 (17%)	0 (0%)	0 (0%)
Invasive mechanical ventilation	285 (27%)	0 (0%)	0 (0%)	487 (9%)

What are the main results?

Critical outcomes

All-cause mortality

Moderate quality evidence from 4 studies found that remdesivir reduces death at day 28 in hospitalised people who require no or low-flow oxygen compared to standard care but the estimate is not statistically significant (25 fewer deaths per 1000 people [RR 0.72, 95% CI 0.52 to 1.01; 6318 people in 4 studies]).

Moderate quality evidence from 3 studies found that remdesivir increases death at day 28 in people who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care but the estimate is not statistically significant (50 more deaths per 1000 people [RR 1.20 CI 95% 0.98 to 1.47; 1004 people in 3 studies]).

Sensitivity analyses for mortality which removed the ACTT-1 trial did not change the overall findings in the full analysis. However, it removed evidence of statistical heterogeneity in the no oxygen/low-flow oxygen supplementation analysis. This could be attributed to the expected differences in the trial based on it being conducted early in the pandemic.

Need for invasive mechanical ventilation of ECMO

Low quality evidence from 1 study found that remdesivir significantly reduced the need for invasive mechanical ventilation (IMV) or ECMO at day 28 with remdesivir compared to standard care in people not receiving IMV at baseline (97 fewer events per 1000 people [RR 0.57 95% CI 0.42 to 0.79; 6192 people in 1 study]).

Serious adverse events

Moderate quality evidence from 3 studies found that remdesivir significantly reduced serious adverse events compared to standard care (63 fewer events per 1000 people [RR 0.75, CI 95% 0.63 to 0.89; 1865 people in 3 studies]).

Important outcomes

Respiratory failure or ARDS

Low quality evidence from 2 studies found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care in hospitalised patients not on invasive ventilation at baseline (30 fewer events per 1000 people [RR 0.79 95% CI 0.35 to 1.78; 1296 people in 2 studies]).

Septic shock

Very low quality evidence from 2 studies found no statistically significant difference in septic shock at day 28 between remdesivir and standard care. (0 fewer events per 1000 people [RR 1.02 95% CI 0.34 to 3.01; 1296 people from 2 studies]).

Clinical recovery

Low quality evidence from 3 studies found no statistically significant difference in clinical recovery at day 28 between remdesivir and standard care (7 fewer events per 1000 people [RR 0.99 95% CI 0.86 to 1.14; 1876 people from 3 studies]). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale (Beigel 2020) or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale (Spinner 2020).

Adverse events

Low quality evidence from 3 studies found no statistically significant difference in adverse events at end of follow up between remdesivir and standard care. (22 more events per 1000 people [RR 1.04 95% CI 0.89 to 1.21; 1880 people from 3 studies]).

Discontinuation due to adverse events

Very low quality evidence from 3 studies found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care. (68 more events per 1000 people [RR 1.73 95% CI 0.57 to 5.28; 1880 people from 3 studies]).

Discharge from hospital

Compared with standard care, remdesivir may have no effect on discharge from hospital at day 28 (7 fewer events per 1000 people [RR 0.99 95% CI 0.96 to 1.03; 5451 people in 1 study]).

Time to recovery

Moderate quality evidence from 1 study found a statistically significant decrease in time to recovery with remdesivir compared with standard care. (HR 1.24, 95% CI 1.08 to 1.42; 1643 people in 2 studies).

Time to improvement

Moderate quality evidence from 2 studies found a borderline statistically significant difference in time to improvement between remdesivir and standard care. (HR 1.17, 95% CI 1.00 to 1.38; 810 people in 2 studies. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale (Spinner 2020) or 6-point ordinal scale (Wang 2020).

Our confidence in the results

Certainty of the evidence is moderate for death in both subgroups (patients who require no oxygen or low-flow oxygen supplementation, and patients who require high-flow oxygen supplementation, NIV or invasive ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or ARDS (due to inconsistency in direction of effect and wide

confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study), clinical recovery and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals). Certainty of the evidence is very low for septic shock (due to non-blinding of patients and personnel, inconsistency in direction of effect and wide confidence intervals).

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality (No oxygen or low flow oxygen) ¹ Within 28 days of commencing treatment 9 Critical	Relative risk 0.72 (CI 95% 0.52 – 1.01) Based on data from 6,318 patients in 4 studies. ² (Randomized controlled)	90 per 1000 Difference:	65 per 1000 25 fewer per 1000 (CI 95% 43 fewer – 1 more)	Moderate Due to serious imprecision ³	A pooled analysis of 6 studies found a non-statistically significant reduction in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving low-flow or no oxygen supplementation
All-cause mortality (High flow oxygen, NIV or IMV) ⁴ Within 28 days of commencing treatment 9 Critical	Relative risk 1.2 (CI 95% 0.98 – 1.47) Based on data from 1,004 patients in 3 studies. ⁵	248 per 1000 Difference:	298 per 1000 50 more per 1000 (CI 95% 5 fewer – 117 more)	Moderate Due to serious imprecision ⁶	A pooled analysis of 4 studies found a non-statistically significant increase in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving high-flow oxygen supplementation, NIV or IMV.
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical	Relative risk 0.57 (CI 95% 0.42 – 0.79) Based on data from 766 patients in 1 studies. ⁷ (Randomized controlled)	225 per 1000 Difference:	128 per 1000 97 fewer per 1000 (CI 95% 130 fewer – 47 fewer)	Low Due to serious imprecision and serious risk of bias ⁸	One study found a statistically significant reduction in the need for invasive mechanical ventilation or ECMO at day 28 with remdesivir compared with standard care, in hospitalised patients not on invasive ventilation at baseline.
Serious adverse events ⁹ End of follow-up 9 Critical	Relative risk 0.75 (CI 95% 0.63 – 0.89) Based on data from 1,865 patients in 3 studies. ¹⁰ (Randomized controlled)	253 per 1000 Difference:	190 per 1000 63 fewer per 1000 (CI 95% 94 fewer – 28 fewer)	Moderate Due to serious risk of bias ¹¹	Three studies found a statistically significant reduction in serious adverse events at end of follow up between remdesivir and standard care.
Respiratory failure or ARDS Within 28 days of commencing treatment	Relative risk 0.79 (CI 95% 0.35 – 1.78) Based on data from 1,296 patients in 2 studies. ¹² (Randomized	143 per 1000 Difference:	113 per 1000 30 fewer per	Low Due to serious inconsistency and serious imprecision ¹³	Two studies found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important	controlled)		1000 (CI 95% 93 fewer – 112 more)		compared with standard care in hospitalised patients not on invasive ventilation at baseline.
Patients requiring ventilation ¹⁴ Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.89 – 1.2) Based on data from 4,964 patients in 1 studies. ¹⁵ (Randomized controlled)	115 per 1000 Difference:	118 per 1000 3 more per 1000 (CI 95% 13 fewer – 23 more)	Moderate Due to serious imprecision ¹⁶	One study found no statistically significant difference in the number of patients requiring mechanical ventilation at day 28 between remdesivir and standard care.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 – 3.01) Based on data from 1,296 patients in 2 studies. ¹⁷ (Randomized controlled)	10 per 1000 Difference:	10 per 1000 0 fewer per 1000 (CI 95% 7 fewer – 20 more)	Very low Due to serious risk of bias, serious inconsistency and serious imprecision ¹⁸	Two studies found no statistically significant difference in septic shock at day 28 between remdesivir and standard care.
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.86 – 1.14) Based on data from 1,876 patients in 3 studies. ¹⁹ (Randomized controlled)	711 per 1000 Difference:	704 per 1000 7 fewer per 1000 (CI 95% 100 fewer – 100 more)	Low Due to serious risk of bias and serious inconsistency ²⁰	Three studies found no statistically significant difference in clinical recovery at day 28 between remdesivir and standard care
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.89 – 1.21) Based on data from 1,880 patients in 3 studies. ²¹ (Randomized controlled)	548 per 1000 Difference:	570 per 1000 22 more per 1000 (CI 95% 60 fewer – 115 more)	Low Due to serious risk of bias and serious inconsistency ²²	Three studies found no statistically significant difference in adverse events at end of follow up between remdesivir and standard care.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.73 (CI 95% 0.57 – 5.28) Based on data from 1,880 patients in 3 studies. ²³ (Randomized controlled)	93 per 1000 Difference:	161 per 1000 68 more per 1000 (CI 95% 40 fewer – 398 more)	Very low Due to serious risk of bias, serious inconsistency and serious imprecision ²⁴	Three studies found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.96 – 1.03) Based on data from 5,451 patients in 1 studies. ²⁵ (Randomized controlled)	720 per 1000 Difference:	713 per 1000 7 fewer per 1000 (CI 95% 29 fewer – 22 more)	Moderate Due to serious imprecision ²⁶	One study found no statistically significant difference in discharge from hospital at day 28 between remdesivir and standard care.

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
Time to recovery Days 6 Important	Hazard Ratio 1.24 (CI 95% 1.08 – 1.42) Based on data from 1,643 patients in 2 studies. ²⁷ (Randomized controlled)			Moderate Due to serious risk of bias ²⁸	Two studies found a statistically significant decrease in time to recovery with remdesivir compared with standard care.
Time to improvement Days 6 Important	Hazard Ratio 1.17 (CI 95% 1 – 1.38) Based on data from 810 patients in 2 studies. ²⁹ (Randomized controlled)			Moderate Due to serious risk of bias ³⁰	Two studies found a borderline statistically significant difference in time to improvement between remdesivir and standard care.

1. People not receiving oxygen or receiving low flow oxygen at baseline only
2. Systematic review [29] with included studies: SOLIDARITY 2020 no O2, Beigel 2020 no O2, Wang 2020 low flow, SOLIDARITY 2020 low/hi flow, Beigel 2020 lo-flow, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
4. People who were receiving high flow oxygen, non-invasive ventilation or invasive mechanical ventilation at baseline
5. Systematic review [29] with included studies: Beigel 2020 hi flow or NIV, SOLIDARITY 2020 ventilation, Beigel 2020 Inv vent, Wang 2020 high flow or ventilation. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
7. Systematic review [29] with included studies: Beigel 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**
9. Listed as critical in PICO
10. Systematic review [29] with included studies: Spinner 2020, Spinner 2020, Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
12. Systematic review [29] with included studies: Beigel 2020, Beigel 2020, Wang 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
14. Listed as critical in PICO
15. Systematic review [29] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
17. Systematic review [29] with included studies: Wang 2020, Beigel 2020. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
19. Systematic review [29] with included studies: Spinner 2020, Spinner 2020, Spinner 2020, Spinner 2020, Beigel 2020,

Beigel 2020, Wang 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.

20. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

21. Systematic review [29] with included studies: Spinner 2020, Beigel 2020, Spinner 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.

22. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

23. Systematic review [29] with included studies: Spinner 2020, Spinner 2020, Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.

24. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**

25. Systematic review [29] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.

26. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**

27. Systematic review [29] . **Baseline/comparator:** Control arm of reference used for intervention.

28. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

29. Systematic review [29] . **Baseline/comparator:** Control arm of reference used for intervention.

30. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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Clinical Question/ PICO

Population: People with COVID-19
Intervention: Remdesivir 5 days
Comparator: Remdesivir 10 days

Summary

There remains uncertainty whether a 5-day course of remdesivir is more effective and safer than a 10-day course.

What is the evidence informing this recommendation?

Evidence comes from two randomised trials that compared 5-day to 10-day treatment with remdesivir in 781 hospitalised patients with moderate to critical COVID-19 (Goldman 2020; Spinner 2020).

Study characteristics

Mean or median age ranged between 56 to 62 years and women comprised 32 to 40% of patients across both studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more.

The majority of people (84%) in 1 trial (Spinner 2020) were not receiving oxygen supplementation at baseline. In the second trial 55% were receiving oxygen supplementation at baseline and 30.5% were ventilated (Goldman 2020).

What are the main results?**Critical outcomes****All-cause mortality**

Moderate quality evidence from 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment (16 fewer deaths per 1000 people [RR 0.73 95% CI 0.40 to 1.33; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment (5 fewer deaths per 1000 people [RR 0.67 95% CI 0.11 to 3.99; 384 people in 1 study]).

Serious adverse events

Moderate quality evidence from 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment (72 fewer events per 1000 people [RR 0.64 95% CI 0.47 to 0.87; 781 people in 2 studies]).

Important outcomes**Acute respiratory failure or ARDS**

Low quality evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment compared to 10-day treatment (62 fewer events per 1000 people [RR 0.47 95% CI 0.24 to 0.94; 397 people in 1 study]).

Septic shock

Very low-quality evidence from 1 study found no statistically significant difference in septic shock at 30 days with remdesivir 5-day treatment compared to 10-day treatment (15 fewer events per 1000 people [RR 0.39 95% CI 0.08 to 2.01; 397 people in 1 study]).

Clinical recovery

Low quality evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment compared to 10-day treatment (108 more events per 1000 people [RR 1.20 95% CI 1.02 to 1.14; 397 people in 1 study]).

Adverse events

Moderate quality evidence from 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment (46 fewer events per 1000 people [RR 0.93 95% CI 0.84 to 1.03; 781 people in 2 studies]).

Discontinuation due to adverse events

Low quality evidence from 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment compared to 10-day treatment (23 fewer events per 1000 people [RR 0.59 95% CI 0.30 to 1.15; 781 people in 2 studies]).

Discharge from hospital

Moderate quality evidence from 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment (38 more events per 1000 people [RR 1.06 95% CI 0.93 to 1.20; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment (9 fewer events per 1000 people [RR 0.99 95% CI 0.92 to

1.06; 384 people in 1 study)).

Our confidence in the results

Certainty of the evidence is moderate for the following outcomes: death within 14 days, serious adverse events, adverse events and discharge from hospital within 14 days. Certainty is low for death within 28 days, acute respiratory failure or ARDS, clinical recovery or discontinuation due to adverse event within 14 days and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation, lack of blinding), serious imprecision (low event rate for the outcome of death within 14 days) and very serious imprecision (reliance on a single study with few patients and/or few events). Certainty of the evidence is very low for septic shock due to lack of blinding and reliance on a single study with few patients and few events.

Outcome Timeframe	Study results and measurements	Comparator Remdesivir 10 days	Intervention Remdesivir 5 days	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality Within 14 days of commencing treatment 9 Critical	Relative risk 0.73 (CI 95% 0.4 – 1.33) Based on data from 781 patients in 2 studies. ¹ (Randomized controlled)	59 per 1000 Difference:	43 per 1000 16 fewer per 1000 (CI 95% 35 fewer – 19 more)	Moderate Due to serious imprecision ²	A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.67 (CI 95% 0.11 – 3.99) Based on data from 384 patients in 1 studies. ³ (Randomized controlled)	16 per 1000 Difference:	11 per 1000 5 fewer per 1000 (CI 95% 14 fewer – 48 more)	Low Due to very serious imprecision ⁴	Evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment.
Serious adverse events End of follow-up 9 Critical	Relative risk 0.64 (CI 95% 0.47 – 0.87) Based on data from 781 patients in 2 studies. ⁵ (Randomized controlled)	200 per 1000 Difference:	128 per 1000 72 fewer per 1000 (CI 95% 106 fewer – 26 fewer)	Moderate Due to serious risk of bias ⁶	A pooled analysis of 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment.
Acute respiratory failure or ARDS Within 30 days of commencing treatment 6 Important	Relative risk 0.47 (CI 95% 0.24 – 0.94) Based on data from 397 patients in 1 studies. ⁷ (Randomized controlled)	117 per 1000 Difference:	55 per 1000 62 fewer per 1000 (CI 95% 89 fewer – 7 fewer)	Low Due to very serious imprecision ⁸	Evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment compared to 10-day treatment.
Septic shock Within 30 days of commencing treatment	Relative risk 0.39 (CI 95% 0.08 – 2.01) Based on data from 397 patients in 1 studies. ⁹	25 per 1000 Difference:	10 per 1000 15 fewer per	Very low Due to very serious imprecision and	Evidence from 1 study found no statistically significant difference in septic shock at 30 days with remdesivir 5-day

Outcome Timeframe	Study results and measurements	Comparator Remdesivir 10 days	Intervention Remdesivir 5 days	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important	(Randomized controlled)		1000 (CI 95% 23 fewer – 25 more)	serious risk of bias ¹⁰	treatment compared to 10-day treatment.
Clinical recovery Within 14 days of commencing treatment 6 Important	Relative risk 1.2 (CI 95% 1.02 – 1.41) Based on data from 397 patients in 1 studies. ¹¹ (Randomized controlled)	538 per 1000 Difference:	646 per 1000 108 more per 1000 (CI 95% 11 more – 221 more)	Low Due to serious risk of bias and serious imprecision ¹²	Evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
Adverse events End of follow-up 6 Important	Relative risk 0.93 (CI 95% 0.84 – 1.03) Based on data from 781 patients in 2 studies. ¹³ (Randomized controlled)	662 per 1000 Difference:	616 per 1000 46 fewer per 1000 (CI 95% 106 fewer – 20 more)	Moderate Due to serious risk of bias ¹⁴	A pooled analysis of 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment.
Discontinued due to adverse event Within 14 days of commencing treatment 6 Important	Relative risk 0.59 (CI 95% 0.3 – 1.15) Based on data from 781 patients in 2 studies. ¹⁵ (Randomized controlled)	56 per 1000 Difference:	33 per 1000 23 fewer per 1000 (CI 95% 39 fewer – 8 more)	Low Due to serious risk of bias and serious imprecision ¹⁶	A pooled analysis of 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
Discharged from hospital Within 14 days of commencing treatment 6 Important	Relative risk 1.06 (CI 95% 0.93 – 1.2) Based on data from 781 patients in 2 studies. ¹⁷ (Randomized controlled)	638 per 1000 Difference:	676 per 1000 38 more per 1000 (CI 95% 45 fewer – 128 more)	Moderate Due to serious risk of bias ¹⁸	A pooled analysis of 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
Discharged from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.92 – 1.06) Based on data from 384 patients in 1 studies. ¹⁹ (Randomized controlled)	902 per 1000 Difference:	893 per 1000 9 fewer per 1000 (CI 95% 72 fewer – 54 more)	Low Due to very serious imprecision ²⁰	Evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment.

1. Systematic review [22] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** due to few events.
3. Systematic review [22] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study, due to few events.
5. Systematic review [22] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. Systematic review [22] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**
9. Systematic review [22] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**
11. Systematic review [22] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
13. Systematic review [22] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
15. Systematic review [22] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** due to few events. **Publication bias: no serious.**
17. Systematic review [22] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
19. Systematic review [22] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**

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Only in research settings

Do not use remdesivir for COVID-19 pneumonia in adults, young people and children in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive mechanical ventilation or invasive mechanical ventilation, except as part of a clinical trial.

Evidence To Decision**Benefits and harms****Important harms**

The panel noted the opposing directions of effect between people receiving high-flow oxygen, non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV), which showed a trend towards higher all-cause mortality, and people receiving low-flow oxygen supplementation or no oxygen, which showed a trend towards lower all-cause mortality. The duration and severity of disease was considered the explanation. The panel were presented with a clinical rationale for antiviral treatment, which supports the thinking that antivirals are expected to be most effective early in the disease course, when viral replication is a driver of disease. Antivirals are less likely to be effective in the later stages in the disease course, which include the hyperinflammatory phase and the need for more respiratory support.

Evidence from randomised controlled trials of remdesivir compared with standard care show that remdesivir has an acceptable safety profile and may reduce the incidence of serious adverse events. However, for people receiving high-flow oxygen supplementation, NIV or IMV there is evidence to suggest that remdesivir may increase 28-day mortality.

Based on the results of 2 studies that compared 10-day with 5-day courses of remdesivir, it is unclear which of these regimens provides the optimal duration of treatment. The current evidence does not suggest any greater benefit for 10-day duration but increased risk of harm. The panel also acknowledged that, if the disease progression resulted in the need for more respiratory support while using remdesivir, there may be no benefit in completing the full course. For these reasons, along with resource impact considerations (see also Resources), the panel agreed to recommend remdesivir for up to 5 days.

The panel noted the unclear additive benefit of remdesivir when used with dexamethasone, particularly because the 2 main trials, SOLIDARITY and ACTT-1, were done before the routine use of dexamethasone.

The panel also reviewed academic-in-confidence data from an observational study but did not consider this to have any effect on the recommendations.

Certainty of the Evidence**Moderate**

Certainty of the evidence is moderate for death in both subgroups (people who need low-flow oxygen supplementation or no oxygen, and people who need high-flow oxygen supplementation, NIV or IMV), all because of serious imprecision (wide confidence intervals). The panel noted difficulties in disaggregating data on different modalities of respiratory support to inform subgroup analysis, with some trials covering both NIV and IMV. However, the panel agreed that subgroup data should be distinguished between high-flow oxygen, NIV or IMV and low-flow oxygen modalities in the pooled meta-analysis of included studies. The panel noted that, despite serious imprecision, the direction of effect was consistently in favour of control across subgroup data covering people on high-flow oxygen, NIV or IMV, suggesting that remdesivir is associated with higher mortality.

Certainty is also moderate for the outcomes of number of people needing ventilation and discharge from hospital (because of reliance on a single study), and serious adverse events, time to recovery and time to improvement (because of non-blinding of people in the trial and personnel).

Certainty of the evidence is low for respiratory failure or acute respiratory distress syndrome (because of inconsistency in direction of effect and wide confidence intervals), number of people needing IMV or extracorporeal membrane oxygenation (because of non-blinding of people in the trial and personnel, and reliance on a single study), clinical recovery and adverse events (because of non-blinding of people in the trial and personnel, and inconsistency in direction of effect) and stopping treatment because of adverse events (because of non-blinding of people in the trial and personnel, and wide confidence intervals). Certainty of the evidence is very low for septic shock (because of non-blinding of people in the trial and

personnel, inconsistency in direction of effect and wide confidence intervals).

Preference and values

We expect few to want the intervention

The panel were not aware of any systematically collected data on peoples' preferences and values. They identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for IMV and serious adverse events. It is likely that these outcomes would also be of similar importance to patients. In addition, other outcomes including less serious adverse events, discharge from hospital, duration of hospital stay and longer-term outcomes such as functional independence are likely to be of particular importance to patients. These outcomes were not as commonly reported in studies.

The panel inferred that, in view of the potential harm for people with COVID-19 receiving high-flow oxygen supplementation, NIV or IMV, most would not choose remdesivir.

Resources

Important issues, or potential issues not investigated

Cost effectiveness was not assessed as part of the evidence review.

The panel raised concerns about opportunity costs where remdesivir is being used in critical care, and the importance of not diverting resources away from best supportive care. The panel noted the value of targeting treatment to optimise use of resources. The panel also noted the lack of evidence showing any benefit of a 10-day over a 5-day regimen, a direction of effect indicating potential harms of the 10-day duration and the resource impact for a longer treatment duration. See also the benefits and harms section.

Equity

Important issues, or potential issues not investigated

The panel noted an absence of evidence on remdesivir use in children. However, they considered unlikely that most children would benefit from this intervention because most children will recover without the need for it. It is also not licensed for use in children under 12 years. Children over 12 years, weighing 40 kg or more, and with adult phenotype disease should have treatment based on the same indications as those used for adults, in particular, if there is progressive respiratory deterioration. Children with comorbidities with significant lung disease may have benefit from treatment with remdesivir, but their treatment should be discussed on a case-by-case basis with the paediatric infectious diseases team.

Children are often excluded from clinical trials. It was suggested that the recommendation could lead to inequity if adults could have remdesivir as part of a trial, but children could not. However, the proposed inequity is outweighed by the possibility of harm from remdesivir use in people who need high-flow or more intensive oxygen therapy.

The panel also noted the absence of evidence on the use of remdesivir in community settings. However, they considered it unlikely that it would be used outside the hospital setting because the criteria for accessing remdesivir in the UK currently stipulate hospitalisation with COVID-19.

No evidence for using remdesivir in pregnancy was identified. The marketing authorisation confirms the lack of evidence and notes that remdesivir should be avoided in pregnancy unless 'the clinical condition of the women requires treatment with it'. People who are pregnant are often excluded from clinical trials, which could lead to inequity if some adults could have remdesivir as part of a clinical trial but people who are pregnant could not. However, the proposed inequity is outweighed by the possibility of harm from remdesivir use in people who need high-flow or more intensive oxygen therapy.

No other equity issues were identified.

Acceptability

Intervention is likely poorly accepted

The panel were not aware of any systematically collected evidence about acceptability. A potential deterring factor to

acceptability could be that the certainty of current evidence is only moderate. However, the panel noted the consistent direction of effect in favour of standard care for those on higher levels of respiratory support.

It is anticipated that, when considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia and need high-flow oxygen supplementation, NIV or IMV would choose not to have remdesivir.

Feasibility

No important issues with the recommended alternative

Although there is no systematically collected evidence about feasibility, the panel noted that current widespread use of remdesivir in clinical practice is an indicator of feasibility.

Rationale

There is evidence that shows remdesivir may increase the risk of death in people who are on high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation. However, the panel were aware of ongoing trials of remdesivir that include this group of people. The panel agreed that remdesivir should only be used for COVID-19 pneumonia in this group as part of a clinical trial to support recruitment into these trials.

Clinical Question/ PICO

Population: People with COVID-19
Intervention: Remdesivir
Comparator: Placebo or standard care

Summary

Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised people who require no or low-flow oxygen.

Compared with standard care, remdesivir probably increases death at day 28 in people who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care.

What is the evidence informing this recommendation?

Evidence comes from 4 randomised controlled trials that compared remdesivir with standard care in 7333 adults hospitalised with COVID-19 (Beigel 2020, Pan 2020, Spinner 2020, Wang 2020). The majority of evidence is from the WHO SOLIDARITY and ACTT-1 trials, which randomised 5451 and 1062 patients with moderate to critical COVID-19 (Pan 2020, Beigel 2020).

The evidence for mortality was divided into 2 analyses based on the level of respiratory support required. This is because it is expected that antivirals will most likely be more effective in the early stages of disease progression. The levels of respiratory support have been used as a proxy to measure disease progression in the trials. Low levels of respiratory support were considered to be no oxygen supplementation or low-flow oxygen supplementation. Higher levels of respiratory support included, high-flow oxygen supplementation, non-invasive ventilation (NIV) [such as Bilevel Positive Airway Pressure (BiPAP) and Continuous Positive Airway Pressure (CPAP)] and invasive ventilation.

The ACTT-1 trial was conducted very early in the pandemic and may not be reflective of current standard care practices. A sensitivity analysis was conducted for key outcomes.

Study characteristics

Mean or median age ranged from 56 to 66 years and women comprised 32 to 44% of patients across the studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more. There was variability in levels of respiratory support among patients included in the trials (see table).

Levels of respiratory support in trial participants

Level of respiratory support	Beigel 2020 (n=1062)	Wang 2020 (n=236)	Spinner 2020 (n=584)	Pan 2020 (n=5451)
No oxygen or low-flow oxygen	573 (54%)	197 (83%)	584 (100%)	4964 (91%)

Level of respiratory support	Biegel 2020 (n=1062)	Wang 2020 (n=236)	Spinner 2020 (n=584)	Pan 2020 (n=5451)
supplementation				
High-flow oxygen supplementation or NIV	193 (18%)	39 (17%)	0 (0%)	0 (0%)
Invasive mechanical ventilation	285 (27%)	0 (0%)	0 (0%)	487 (9%)

What are the main results?

Critical outcomes

All-cause mortality

Moderate quality evidence from 4 studies found that remdesivir reduces death at day 28 in hospitalised people who require no or low-flow oxygen compared to standard care but the estimate is not statistically significant (25 fewer deaths per 1000 people [RR 0.72, 95% CI 0.52 to 1.01; 6318 people in 4 studies]).

Moderate quality evidence from 3 studies found that remdesivir increases death at day 28 in people who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care but the estimate is not statistically significant (50 more deaths per 1000 people [RR 1.20 CI 95% 0.98 to 1.47; 1004 people in 3 studies]).

Sensitivity analyses for mortality which removed the ACTT-1 trial did not change the overall findings in the full analysis. However, it removed evidence of statistical heterogeneity in the no oxygen/low-flow oxygen supplementation analysis. This could be attributed to the expected differences in the trial based on it being conducted early in the pandemic.

Need for invasive mechanical ventilation of ECMO

Low quality evidence from 1 study found that remdesivir significantly reduced the need for invasive mechanical ventilation (IMV) or ECMO at day 28 with remdesivir compared to standard care in people not receiving IMV at baseline (97 fewer events per 1000 people [RR 0.57 95% CI 0.42 to 0.79; 6192 people in 1 study]).

Serious adverse events

Moderate quality evidence from 3 studies found that remdesivir significantly reduced serious adverse events compared to standard care (63 fewer events per 1000 people [RR 0.75, CI 95% 0.63 to 0.89; 1865 people in 3 studies]).

Important outcomes

Respiratory failure or ARDS

Low quality evidence from 2 studies found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care in hospitalised patients not on invasive ventilation at baseline (30 fewer events per 1000 people [RR 0.79 95% CI 0.35 to 1.78; 1296 people in 2 studies]).

Septic shock

Very low quality evidence from 2 studies found no statistically significant difference in septic shock at day 28 between remdesivir and standard care. (0 fewer events per 1000 people [RR 1.02 95% CI 0.34 to 3.01; 1296 people from 2 studies]).

Clinical recovery

Low quality evidence from 3 studies found no statistically significant difference in clinical recovery at day 28 between remdesivir and standard care (7 fewer events per 1000 people [RR 0.99 95% CI 0.86 to 1.14; 1876 people from 3 studies]). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale (Beigel 2020) or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale (Spinner 2020).

Adverse events

Low quality evidence from 3 studies found no statistically significant difference in adverse events at end of follow up between remdesivir and standard care. (22 more events per 1000 people [RR 1.04 95% CI 0.89 to 1.21; 1880 people from 3 studies]).

Discontinuation due to adverse events

Very low quality evidence from 3 studies found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care. (68 more events per 1000 people [RR 1.73 95% CI 0.57 to 5.28; 1880 people from 3 studies]).

Discharge from hospital

Compared with standard care, remdesivir may have no effect on discharge from hospital at day 28 (7 fewer events per 1000 people [RR 0.99 95% CI 0.96 to 1.03; 5451 people in 1 study]).

Time to recovery

Moderate quality evidence from 1 study found a statistically significant decrease in time to recovery with remdesivir compared with standard care. (HR 1.24, 95% CI 1.08 to 1.42; 1643 people in 2 studies).

Time to improvement

Moderate quality evidence from 2 studies found a borderline statistically significant difference in time to improvement between remdesivir and standard care. (HR 1.17, 95% CI 1.00 to 1.38; 810 people in 2 studies. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale (Spinner 2020) or 6-point ordinal scale (Wang 2020)).

Our confidence in the results

Certainty of the evidence is moderate for death in both subgroups (patients who require no oxygen or low-flow oxygen supplementation, and patients who require high-flow oxygen supplementation, NIV or invasive ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or ARDS (due to inconsistency in direction of effect and wide confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study), clinical recovery and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals). Certainty of the evidence is very low for septic shock (due to non-blinding of patients and personnel, inconsistency in direction of effect and wide confidence intervals).

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality (No oxygen or low flow oxygen) ¹ Within 28 days of commencing treatment 9 Critical	Relative risk 0.72 (CI 95% 0.52 – 1.01) Based on data from 6,318 patients in 4 studies. ² (Randomized controlled)	90 per 1000 Difference:	65 per 1000 25 fewer per 1000 (CI 95% 43 fewer – 1 more)	Moderate Due to serious imprecision ³	A pooled analysis of 6 studies found a non-statistically significant reduction in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving low-flow or no oxygen supplementation
All-cause mortality (High flow oxygen, NIV or IMV) ⁴ Within 28 days of commencing treatment 9 Critical	Relative risk 1.2 (CI 95% 0.98 – 1.47) Based on data from 1,004 patients in 3 studies. ⁵	248 per 1000 Difference:	298 per 1000 50 more per 1000 (CI 95% 5 fewer – 117 more)	Moderate Due to serious imprecision ⁶	A pooled analysis of 4 studies found a non-statistically significant increase in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving high-flow oxygen supplementation, NIV or IMV.
Invasive mechanical ventilation or ECMO	Relative risk 0.57 (CI 95% 0.42 – 0.79) Based on data from 766 patients in 1 studies. ⁷	225 per 1000 Difference:	128 per 1000 97 fewer per	Low Due to serious imprecision and serious risk of bias	One study found a statistically significant reduction in the need for invasive mechanical

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
Within 28 days of commencing treatment 9 Critical	(Randomized controlled)		1000 (CI 95% 130 fewer — 47 fewer)	8	ventilation or ECMO at day 28 with remdesivir compared with standard care, in hospitalised patients not on invasive ventilation at baseline.
Serious adverse events ⁹ End of follow-up 9 Critical	Relative risk 0.75 (CI 95% 0.63 — 0.89) Based on data from 1,865 patients in 3 studies. ¹⁰ (Randomized controlled)	253 per 1000 Difference:	190 per 1000 63 fewer per 1000 (CI 95% 94 fewer — 28 fewer)	Moderate Due to serious risk of bias ¹¹	Three studies found a statistically significant reduction in serious adverse events at end of follow up between remdesivir and standard care.
Respiratory failure or ARDS Within 28 days of commencing treatment 6 Important	Relative risk 0.79 (CI 95% 0.35 — 1.78) Based on data from 1,296 patients in 2 studies. ¹² (Randomized controlled)	143 per 1000 Difference:	113 per 1000 30 fewer per 1000 (CI 95% 93 fewer — 112 more)	Low Due to serious inconsistency and serious imprecision ¹³	Two studies found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care in hospitalised patients not on invasive ventilation at baseline.
Patients requiring ventilation ¹⁴ Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.89 — 1.2) Based on data from 4,964 patients in 1 studies. ¹⁵ (Randomized controlled)	115 per 1000 Difference:	118 per 1000 3 more per 1000 (CI 95% 13 fewer — 23 more)	Moderate Due to serious imprecision ¹⁶	One study found no statistically significant difference in the number of patients requiring mechanical ventilation at day 28 between remdesivir and standard care.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 patients in 2 studies. ¹⁷ (Randomized controlled)	10 per 1000 Difference:	10 per 1000 0 fewer per 1000 (CI 95% 7 fewer — 20 more)	Very low Due to serious risk of bias, serious inconsistency and serious imprecision ¹⁸	Two studies found no statistically significant difference in septic shock at day 28 between remdesivir and standard care.
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 patients in 3 studies. ¹⁹ (Randomized controlled)	711 per 1000 Difference:	704 per 1000 7 fewer per 1000 (CI 95% 100 fewer — 100 more)	Low Due to serious risk of bias and serious inconsistency ²⁰	Three studies found no statistically significant difference in clinical recovery at day 28 between remdesivir and standard care
Adverse events End of follow-up	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 1,880 patients in 3	548 per 1000	570 per 1000	Low Due to serious risk of bias and serious	Three studies found no statistically significant difference in adverse events at end of follow

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important	studies. ²¹ (Randomized controlled)	Difference:	22 more per 1000 (CI 95% 60 fewer – 115 more)	inconsistency ²²	up between remdesivir and standard care.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.73 (CI 95% 0.57 – 5.28) Based on data from 1,880 patients in 3 studies. ²³ (Randomized controlled)	93 per 1000 Difference:	161 per 1000 68 more per 1000 (CI 95% 40 fewer – 398 more)	Very low Due to serious risk of bias, serious inconsistency and serious imprecision ²⁴	Three studies found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.96 – 1.03) Based on data from 5,451 patients in 1 studies. ²⁵ (Randomized controlled)	720 per 1000 Difference:	713 per 1000 7 fewer per 1000 (CI 95% 29 fewer – 22 more)	Moderate Due to serious imprecision ²⁶	One study found no statistically significant difference in discharge from hospital at day 28 between remdesivir and standard care.
Time to recovery Days 6 Important	Hazard Ratio 1.24 (CI 95% 1.08 – 1.42) Based on data from 1,643 patients in 2 studies. ²⁷ (Randomized controlled)			Moderate Due to serious risk of bias ²⁸	Two studies found a statistically significant decrease in time to recovery with remdesivir compared with standard care.
Time to improvement Days 6 Important	Hazard Ratio 1.17 (CI 95% 1 – 1.38) Based on data from 810 patients in 2 studies. ²⁹ (Randomized controlled)			Moderate Due to serious risk of bias ³⁰	Two studies found a borderline statistically significant difference in time to improvement between remdesivir and standard care.

1. People not receiving oxygen or receiving low flow oxygen at baseline only
2. Systematic review [29] with included studies: SOLIDARITY 2020 no O2, Beigel 2020 no O2, Wang 2020 low flow, SOLIDARITY 2020 low/hi flow, Beigel 2020 lo-flow, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
4. People who were receiving high flow oxygen, non-invasive ventilation or invasive mechanical ventilation at baseline
5. Systematic review [29] with included studies: Beigel 2020 hi flow or NIV, SOLIDARITY 2020 ventilation, Beigel 2020 Inv vent, Wang 2020 high flow or ventilation. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
7. Systematic review [29] with included studies: Beigel 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**
9. Listed as critical in PICO

10. Systematic review [29] with included studies: Spinner 2020, Spinner 2020, Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
12. Systematic review [29] with included studies: Beigel 2020, Beigel 2020, Wang 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
14. Listed as critical in PICO
15. Systematic review [29] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
17. Systematic review [29] with included studies: Wang 2020, Beigel 2020. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
19. Systematic review [29] with included studies: Spinner 2020, Spinner 2020, Spinner 2020, Spinner 2020, Beigel 2020, Beigel 2020, Wang 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
21. Systematic review [29] with included studies: Spinner 2020, Beigel 2020, Spinner 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
23. Systematic review [29] with included studies: Spinner 2020, Spinner 2020, Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
24. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
25. Systematic review [29] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
26. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
27. Systematic review [29] . **Baseline/comparator:** Control arm of reference used for intervention.
28. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
29. Systematic review [29] . **Baseline/comparator:** Control arm of reference used for intervention.
30. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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Clinical Question/ PICO

Population: People with COVID-19
Intervention: Remdesivir 5 days
Comparator: Remdesivir 10 days

Summary

There remains uncertainty whether a 5-day course of remdesivir is more effective and safer than a 10-day course.

What is the evidence informing this recommendation?

Evidence comes from two randomised trials that compared 5-day to 10-day treatment with remdesivir in 781 hospitalised patients with moderate to critical COVID-19 (Goldman 2020; Spinner 2020).

Study characteristics

Mean or median age ranged between 56 to 62 years and women comprised 32 to 40% of patients across both studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more.

The majority of people (84%) in 1 trial (Spinner 2020) were not receiving oxygen supplementation at baseline. In the second trial 55% were receiving oxygen supplementation at baseline and 30.5% were ventilated (Goldman 2020).

What are the main results?

Critical outcomes

All-cause mortality

Moderate quality evidence from 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment (16 fewer deaths per 1000 people [RR 0.73 95% CI 0.40 to 1.33; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment (5 fewer deaths per 1000 people [RR 0.67 95% CI 0.11 to 3.99; 384 people in 1 study]).

Serious adverse events

Moderate quality evidence from 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment (72 fewer events per 1000 people [RR 0.64 95% CI 0.47 to 0.87; 781 people in 2 studies]).

Important outcomes

Acute respiratory failure or ARDS

Low quality evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment compared to 10-day treatment (62 fewer events per 1000 people [RR 0.47 95% CI 0.24 to 0.94; 397 people in 1 study]).

Septic shock

Very low-quality evidence from 1 study found no statistically significant difference in septic shock at 30 days with remdesivir 5-day treatment compared to 10-day treatment (15 fewer events per 1000 people [RR 0.39 95% CI 0.08 to 2.01; 397 people in 1 study]).

Clinical recovery

Low quality evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment compared to 10-day treatment (108 more events per 1000 people [RR 1.20 95% CI 1.02 to 1.14; 397 people in 1 study]).

Adverse events

Moderate quality evidence from 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment (46 fewer events per 1000 people [RR 0.93 95% CI 0.84 to 1.03; 781 people in 2 studies]).

Discontinuation due to adverse events

Low quality evidence from 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment compared to 10-day treatment (23 fewer events per 1000 people [RR 0.59 95% CI 0.30 to 1.15; 781 people in 2 studies]).

Discharge from hospital

Moderate quality evidence from 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment (38 more events per 1000 people [RR 1.06 95% CI 0.93 to 1.20; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment (9 fewer events per 1000 people [RR 0.99 95% CI 0.92 to 1.06; 384 people in 1 study]).

Our confidence in the results

Certainty of the evidence is moderate for the following outcomes: death within 14 days, serious adverse events, adverse events and discharge from hospital within 14 days. Certainty is low for death within 28 days, acute respiratory failure or ARDS, clinical recovery or discontinuation due to adverse event within 14 days and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation, lack of blinding), serious imprecision (low event rate for the outcome of death within 14 days) and very serious imprecision (reliance on a single study with few patients and/or few events). Certainty of the evidence is very low for septic shock due to lack of blinding and reliance on a single study with few patients and few events.

Outcome Timeframe	Study results and measurements	Comparator Remdesivir 10 days	Intervention Remdesivir 5 days	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality Within 14 days of commencing treatment 9 Critical	Relative risk 0.73 (CI 95% 0.4 – 1.33) Based on data from 781 patients in 2 studies. ¹ (Randomized controlled)	59 per 1000 Difference:	43 per 1000 16 fewer per 1000 (CI 95% 35 fewer – 19 more)	Moderate Due to serious imprecision ²	A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.67 (CI 95% 0.11 – 3.99) Based on data from 384 patients in 1 studies. ³ (Randomized controlled)	16 per 1000 Difference:	11 per 1000 5 fewer per 1000 (CI 95% 14 fewer – 48 more)	Low Due to very serious imprecision ⁴	Evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment.

Outcome Timeframe	Study results and measurements	Comparator Remdesivir 10 days	Intervention Remdesivir 5 days	Certainty of the Evidence (Quality of evidence)	Plain language summary
Serious adverse events End of follow-up 9 Critical	Relative risk 0.64 (CI 95% 0.47 – 0.87) Based on data from 781 patients in 2 studies. ⁵ (Randomized controlled)	200 per 1000 Difference:	128 per 1000 72 fewer per 1000 (CI 95% 106 fewer – 26 fewer)	Moderate Due to serious risk of bias ⁶	A pooled analysis of 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment.
Acute respiratory failure or ARDS Within 30 days of commencing treatment 6 Important	Relative risk 0.47 (CI 95% 0.24 – 0.94) Based on data from 397 patients in 1 studies. ⁷ (Randomized controlled)	117 per 1000 Difference:	55 per 1000 62 fewer per 1000 (CI 95% 89 fewer – 7 fewer)	Low Due to very serious imprecision ⁸	Evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment compared to 10-day treatment.
Septic shock Within 30 days of commencing treatment 6 Important	Relative risk 0.39 (CI 95% 0.08 – 2.01) Based on data from 397 patients in 1 studies. ⁹ (Randomized controlled)	25 per 1000 Difference:	10 per 1000 15 fewer per 1000 (CI 95% 23 fewer – 25 more)	Very low Due to very serious imprecision and serious risk of bias ¹⁰	Evidence from 1 study found no statistically significant difference in septic shock at 30 days with remdesivir 5-day treatment compared to 10-day treatment.
Clinical recovery Within 14 days of commencing treatment 6 Important	Relative risk 1.2 (CI 95% 1.02 – 1.41) Based on data from 397 patients in 1 studies. ¹¹ (Randomized controlled)	538 per 1000 Difference:	646 per 1000 108 more per 1000 (CI 95% 11 more – 221 more)	Low Due to serious risk of bias and serious imprecision ¹²	Evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
Adverse events End of follow-up 6 Important	Relative risk 0.93 (CI 95% 0.84 – 1.03) Based on data from 781 patients in 2 studies. ¹³ (Randomized controlled)	662 per 1000 Difference:	616 per 1000 46 fewer per 1000 (CI 95% 106 fewer – 20 more)	Moderate Due to serious risk of bias ¹⁴	A pooled analysis of 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment.
Discontinued due to adverse event Within 14 days of commencing treatment 6 Important	Relative risk 0.59 (CI 95% 0.3 – 1.15) Based on data from 781 patients in 2 studies. ¹⁵ (Randomized controlled)	56 per 1000 Difference:	33 per 1000 23 fewer per 1000 (CI 95% 39 fewer – 8 more)	Low Due to serious risk of bias and serious imprecision ¹⁶	A pooled analysis of 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment compared to 10-day treatment.

Outcome Timeframe	Study results and measurements	Comparator Remdesivir 10 days	Intervention Remdesivir 5 days	Certainty of the Evidence (Quality of evidence)	Plain language summary
Discharged from hospital Within 14 days of commencing treatment 6 Important	Relative risk 1.06 (CI 95% 0.93 – 1.2) Based on data from 781 patients in 2 studies. ¹⁷ (Randomized controlled)	638 per 1000 Difference:	676 per 1000 38 more per 1000 (CI 95% 45 fewer – 128 more)	Moderate Due to serious risk of bias ¹⁸	A pooled analysis of 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
Discharged from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.92 – 1.06) Based on data from 384 patients in 1 studies. ¹⁹ (Randomized controlled)	902 per 1000 Difference:	893 per 1000 9 fewer per 1000 (CI 95% 72 fewer – 54 more)	Low Due to very serious imprecision ²⁰	Evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment.

1. Systematic review [22] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** due to few events.
3. Systematic review [22] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study, due to few events.
5. Systematic review [22] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. Systematic review [22] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**
9. Systematic review [22] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**
11. Systematic review [22] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
13. Systematic review [22] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
15. Systematic review [22] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious.**

Indirectness: no serious. Imprecision: serious. due to few events. **Publication bias: no serious.**

17. Systematic review [22] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious.**

Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.

19. Systematic review [22] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.

20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**

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26. Spinner CD, Gottlieb RL, Criner GJ, Arribas Lopez JR, Cattelan AM, Soriano Viladomiu A., et al. : Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. Jama 2020;324(11):1048-1057 [Journal](#)

7.4 Tocilizumab

Info Box

Definition

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the [Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'](#).

Recommended

Updated

Offer tocilizumab to adults in hospital with COVID-19 if all the following apply:

- they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
- they have not had another interleukin-6 inhibitor during this admission
- there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab.

And they:

- need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
- are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

In October 2021, the marketing authorisations for tocilizumab do not cover use in COVID-19. See [NICE's information on prescribing medicines for more about off-label and unlicensed use of medicines](#).

The recommended dosage for tocilizumab is a single dose of 8 mg/kg by intravenous infusion. The total dose should not exceed 800 mg.

For tocilizumab use in pregnancy, follow the [Royal College of Obstetrics and Gynaecology guidance on coronavirus \(COVID-19\) infection and pregnancy](#).

For full details of adverse events and contraindications, see the summaries of product characteristics for tocilizumab.

See [NHS England's Interim Clinical Commissioning Policy on tocilizumab for hospitalised patients with COVID-19 pneumonia \(adults\)](#) for further information.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Available evidence suggests that tocilizumab plus standard care is statistically significantly more effective than standard care alone at reducing all-cause mortality at 21 to 28 days in adults in hospital with COVID-19. Tocilizumab plus standard care did not statistically significantly reduce mortality at other timepoints compared with standard care alone, although the panel noted that considerably fewer people were included at the other timepoints.

The evidence suggests that people having tocilizumab plus standard care have statistically significantly fewer serious adverse events compared with people having standard care alone. Serious adverse events reported in the studies included bacterial infection and acute respiratory distress syndrome. The panel acknowledged that the reason for this reduction is not clear but suggested it may be because of a beneficial effect of tocilizumab.

The evidence also suggests that tocilizumab plus standard care is statistically significantly more effective than standard care alone at reducing the combined outcome of death and time on organ support.

The panel noted that standard care varied across trials. In particular, corticosteroids were not offered routinely in trials carried out before the results of the dexamethasone arm of the RECOVERY trial were published. The panel discussed that the evidence shows an additional benefit when tocilizumab is used with corticosteroids. About two-thirds of people across all studies had corticosteroids.

Long-term use of tocilizumab for non-COVID indications is associated with the risk of opportunistic infections because of its effect on the immune system. The panel acknowledged that most people in the trials had a single dose of tocilizumab. Therefore, the risks associated with long-term use may not apply to people having tocilizumab for COVID-19. The studies had follow-up periods of between 14 and 90 days, so should have captured any adverse events of tocilizumab. The panel acknowledged the suppressive effect that tocilizumab can have on C-reactive protein levels, which is important for ongoing care after treatment. To identify serious adverse reactions to tocilizumab, there is a [Yellow Card reporting system for the Medicines and Healthcare products Regulatory Agency](#) in place. Details of special warnings and precautions for tocilizumab use are in its summaries of product characteristics. The panel also agreed that it would be beneficial to ensure that ongoing care providers in the community are informed about people's treatments when they are transferred from a hospital setting.

This is so that they are aware of any potential long-term treatment effects.

Certainty of the Evidence

Moderate

The certainty of the evidence ranges from high to low. All-cause mortality at 21 to 28 days is of high quality. The certainty of all-cause mortality at other timepoints is moderate because of wide confidence intervals.

The serious adverse events result is of moderate quality because of a lack of blinding. The adverse events data is of low quality because of a lack of blinding and a wide confidence interval.

There is a moderate risk of bias with the combined outcome of reducing death and reducing time on organ support because of a lack of blinding.

None of the outcomes have been downgraded for indirectness. This is because the largest randomised controlled trial contributing to the evidence base was carried out in the UK. Therefore, the panel considered that the population in the trial is generalisable to the UK context and representative of people admitted to hospital in the UK. Although eligibility criteria varied across the studies, there were few restrictions in the entry criteria for RECOVERY because it was a pragmatic trial. The restrictions included other active infection or hypersensitivity to tocilizumab, which reflects the summaries of product characteristics for tocilizumab.

Preference and values

No substantial variability expected

The panel identified critical outcomes that would be important for decision making. These included all-cause mortality and serious adverse events. It is likely that these outcomes would also be of similar importance to people with COVID-19. In addition, less serious adverse events are likely to be of particular importance to people with COVID-19. This outcome was not as commonly reported in studies.

Resources

Important issues, or potential issues not investigated

The panel commented that a recommendation offering tocilizumab may be dependent on its availability across different hospitals. They also acknowledged that the eligibility criteria in the commissioning policy for tocilizumab use allows people with COVID-19 to have treatment as early as possible. This may reduce the need to use more critical resources in the hospital setting. For further details, see [NHS England's Interim Clinical Commissioning Policy on tocilizumab for hospitalised patients with COVID-19 pneumonia \(adults\)](#).

Equity

Important issues, or potential issues not investigated

The trials identified do not provide data on tocilizumab use in pregnancy, or in children and young people. While the evidence base is limited, there is currently no evidence that tocilizumab is teratogenic or fetotoxic. Therefore, the decision about whether someone who is pregnant meets the eligibility criteria should be considered by a multidisciplinary team that includes an obstetric specialist when possible. The summaries of product characteristics outline special considerations for breastfeeding and conception.

The panel discussed that oxygen supplementation may not be suitable for everyone. Although this may be more of an issue in the community, the panel wanted to ensure that tocilizumab use is not reliant on having oxygen supplementation. Rather, they agreed that there should be a need for oxygen supplementation.

No evidence has been identified that evaluated the efficacy of tocilizumab in groups of people with other protected characteristics such as ethnicity

Acceptability

Important issues, or potential issues not investigated

No evidence was identified that could be used to assess the acceptability of tocilizumab use. However, in the context of the COVID-19 pandemic, it is likely that patients, and their families and clinicians, would accept tocilizumab use because the benefits of reducing death and days on organ support seem to outweigh the risk of adverse events.

Feasibility

No important issues with the recommended alternative

The trials were all carried out in a hospital setting. The panel considered this to be appropriate and agreed that it reflects current practice for use and availability of tocilizumab.

Rationale

There is evidence that tocilizumab plus standard care reduces both all-cause mortality and time on organ support compared with standard care alone. Corticosteroids are now part of standard care for people with COVID-19, and there is evidence of an additional benefit when tocilizumab is also used. The entry criteria for the RECOVERY and REMAP-CAP trials were representative of people admitted to hospital in the UK, so the eligibility criteria for tocilizumab use are based on these trials.

The entry criteria for RECOVERY were:

- clinically suspected or microbiologically confirmed COVID-19
- low oxygen levels
- C-reactive protein levels of more than 75 mg/litre.

The entry criteria for REMAP-CAP were:

- clinically suspected or microbiologically confirmed COVID-19
- severe disease state, defined by receiving respiratory or cardiovascular organ failure support in an intensive care unit.

Respiratory organ support was defined as invasive or non-invasive mechanical ventilation, including via a high-flow nasal cannula if flow rate was more than 30 litres/min and fraction of inspired oxygen was less than 0.4. The criteria for severe disease state were still met if non-invasive ventilation would normally have been provided but was being withheld because of infection control concerns associated with aerosol generating procedures.

Cardiovascular organ support was defined as the intravenous infusion of any vasopressor or inotrope.

Clinical Question/ PICO

Population:	People with COVID-19
Intervention:	Tocilizumab
Comparator:	Standard care or placebo

Summary

Tocilizumab decreases the risk of death in hospitalised people at 21 to 28 days. However, there is uncertainty for this outcome at other timepoints. Tocilizumab decreases the number of hospitalised people experiencing serious adverse events.

What is the evidence informing this recommendation?

Evidence comes from eleven randomised trials that compared tocilizumab with standard care or placebo in 7599 adults hospitalised with COVID-19 (Hermine 2020, Hermine 2021, RECOVERY 2021, REMAP-CAP 2021, Rosas 2021, Salama 2020, Salvarani 2020, Soin 2021, Stone 2020, Veiga 2020, Wang 2020). This is an update to the March 2021 review. During this update, we have added an extra study (Hermine 2021) and updated two studies with more recent data (REMAP-CAP 2021 and RECOVERY 2021).

The strongest evidence for prescribing tocilizumab comes from the high quality all-cause mortality data at day 21 to 28 where tocilizumab reduces mortality for hospitalised patients with COVID-19. The all-cause mortality data could not differentiate between tocilizumab and control for day 14 (n=450), day 60 (n=450), or day 90 (n=1802).

This evidence is supported by the high quality serious adverse events data, collected at the end of 9 studies, where

tocilizumab has a lower number of hospitalised people experiencing serious adverse events compared to the control arms.

The REMAP-CAP study's ordinal scale combined in-hospital mortality (to day 90) and days free of organ support up to day 21, and favoured tocilizumab compared to control.

Publication status

Three studies are only available as preprints (Rosas 2021 posted to medRxiv on 12 September 2020, REMAP-CAP 2021 posted to medRxiv on 9 January 2021, and RECOVERY 2021 posted to medRxiv on 11 February 2021) and have therefore not been peer reviewed.

Study characteristics

Mean or median age ranged from 55 to 64 years and women comprised 14 to 50% of patients across the studies. Pregnant and breastfeeding women were ineligible except for the RECOVERY trial which included 3 pregnant women. Studies included patients with moderate, severe, and critical COVID-19 (see table).

There was variability in disease severity among patients included in the trials (see table). Standard care varied across studies. Some of the earlier trials were conducted or published before the results of the dexamethasone arm of the RECOVERY trial were published which meant that corticosteroids were not routinely given across all studies.

Disease severity in trial participants

Disease severity	Number of patients	References
Moderate-Severe	4959	Wang 2020, Hermine 2020, Hermine 2021, Stone 2020, Salvarani 2020, Salama 2020, RECOVERY 2021, Soin 2021
Moderate-Critical	567	Rosas 2021, Veiga 2020
Critical	1317	REMAP-CAP 2021, RECOVERY 2021

What are the main results?

Tocilizumab decreases the risk of death in hospitalised people at 21 to 28 days (28 fewer per 100 people: RR 0.90 CI 95% 0.83 - 0.98; 6182 patients in 9 studies). However, there is uncertainty for this outcome at other timepoints (day 14, day 60, and day 90). Tocilizumab decreases the number of hospitalised people experiencing serious adverse events (37 fewer per 1000 people: RR 0.83 CI 95% 0.72 - 0.95; 3364 patients in 9 studies) but probably has little impact on adverse events (30 more per 1000 people: RR 1.06 CI 95% 0.90 - 1.24; 2012 patients in 8 studies).

Our confidence in the results

Certainty of the evidence is high for mortality at 21 to 28 days but not for the other mortality timepoints. Certainty of the evidence is high for serious adverse events. Certainty of the evidence is moderate for adverse events because it was downgraded for imprecision as the 95% confidence interval crossed the line of no effect. Certainty of the evidence was moderate for 'days free of organ support' and for the 'ordinal scale combining in-hospital mortality and days free of organ support'. This is because these two outcomes were downgraded for serious risk of bias.

Outcome Timeframe	Study results and measurements	Comparator Standard care or placebo	Intervention Tocilizumab	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality [All patients] Day 14 after commencing treatment 9 Critical	Relative risk 1.01 (CI 95% 0.46 – 2.2) Based on data from 450 patients in 1 studies. ¹ (Randomized controlled)	50 per 1000 Difference:	51 per 1000 1 more per 1000 (CI 95% 27 fewer – 60 more)	Moderate Due to serious imprecision ²	One study found no statistically significant difference in mortality at 14 days with tocilizumab compared with control
All-cause mortality [All patients]	Relative risk 0.9 (CI 95% 0.83 – 0.98) Based on data from 6,182 patients in 9	278 per 1000	250 per 1000	High	The pooled estimate of nine studies found that tocilizumab decreased death in hospitalised

Outcome Timeframe	Study results and measurements	Comparator Standard care or placebo	Intervention Tocilizumab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Day 21-28 after commencing treatment 9 Critical	studies. ³ (Randomized controlled)	Difference:	28 fewer per 1000 (CI 95% 47 fewer – 6 fewer)		patients at 21 to 28 days compared with control
All-cause mortality [All patients] Day 60 after commencing treatment 9 Critical	Relative risk 0.75 (CI 95% 0.41 – 1.36) Based on data from 450 patients in 1 studies. ⁴ (Randomized controlled)	102 per 1000 Difference:	77 per 1000 25 fewer per 1000 (CI 95% 60 fewer – 37 more)	Moderate Due to serious imprecision ⁵	One study found no statistically significant difference in mortality at 60 days with tocilizumab compared with control
All-cause mortality [All patients] Day 90 after commencing treatment 9 Critical	Relative risk 0.89 (CI 95% 0.77 – 1.04) Based on data from 1,798 patients in 2 studies. ⁶ (Randomized controlled)	276 per 1000 Difference:	246 per 1000 30 fewer per 1000 (CI 95% 63 fewer – 11 more)	Moderate Due to serious imprecision ⁷	The pooled estimate of two studies found no statistically significant difference in mortality at 90 days with tocilizumab compared with control
Serious adverse events At day 14 to day 90 9 Critical	Relative risk 0.83 (CI 95% 0.72 – 0.95) Based on data from 3,364 patients in 9 studies. ⁸ (Randomized controlled)	217 per 1000 Difference:	180 per 1000 37 fewer per 1000 (CI 95% 61 fewer – 11 fewer)	Moderate Because of risk of bias due to lack of blinding ⁹	The pooled estimate of nine studies found that there were fewer serious adverse events in the tocilizumab arm at day 14 to day 90 compared with control
Adverse events At day 14 to day 90 6 Important	Relative risk 1.06 (CI 95% 0.9 – 1.24) Based on data from 2,012 patients in 8 studies. ¹⁰ (Randomized controlled)	507 per 1000 Difference:	537 per 1000 30 more per 1000 (CI 95% 51 fewer – 122 more)	Low Because of serious risk of bias due to lack of blinding, and due to serious imprecision ¹¹	The pooled estimate of eight studies found no statistically significant difference in adverse events at day 14 to day 90 between tocilizumab and control
Ordinal scale combining in- hospital mortality and days free of organ support In hospital mortality at day 90 and days free of organ support at day 21 4 Important	Based on data from: 1,352 patients in 1 studies. (Randomized controlled)	Median adjusted odds ratio 1.46 (95% CI 1.13 - 1.88)		Moderate Because of serious risk of bias due to lack of blinding ¹²	One study that had an ordinal scale combining in-hospital mortality at 90 days and days free of organ support to 21 days favoured tocilizumab compared with usual care

Outcome Timeframe	Study results and measurements	Comparator Standard care or placebo	Intervention Tocilizumab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Days free of organ support in survivors Day 21 after commencing treatment 4 Important	Based on data from: 1,352 patients in 1 studies. ¹³ (Randomized controlled)	Tocilizumab (median): 15 days (IQR 7.25 - 18), usual care: 13 days (IQR 4 - 17)		Moderate Because of serious risk of bias due to lack of blinding ¹⁴	One study found that tocilizumab increased days free of organ support compared with usual care at 21 days

1. Systematic review with included studies: [96]. **Baseline/comparator:** Systematic review.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
3. Systematic review [40] with included studies: [96], Rosas 2020, Soin 2021, [98], Veiga 2021, Hermine 2020, Salvarini 2020, Stone 2020, Salama 2020. **Baseline/comparator:** Systematic review.
4. Systematic review with included studies: [96]. **Baseline/comparator:** Systematic review.
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The 95% CI crosses the line of no effect. **Publication bias: no serious.**
6. Systematic review with included studies: [97], [96]. **Baseline/comparator:** Systematic review.
7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The 95% CI crosses the line of no effect. **Publication bias: no serious.**
8. Systematic review [40] with included studies: Veiga 2021, Hermine 2020, [97], Salama 2020, Rosas 2020, Wang 2020, Stone 2020, Soin 2021, [96]. **Baseline/comparator:** Systematic review.
9. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10. Systematic review [40] with included studies: Stone 2020, Rosas 2020, [41], Veiga 2021, Hermine 2020, Wang 2020, Salama 2020, [96]. **Baseline/comparator:** Systematic review.
11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The 95% CI crosses the line of no effect. **Publication bias: no serious.**
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
13. Primary study **Supporting references:** [97],
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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Only in research settings

Consider tocilizumab for children and young people who have severe COVID-19 or paediatric inflammatory multisystem syndrome only if they are 1 year and over, and only in the context of a clinical trial.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

No evidence on tocilizumab use in children was identified. However, the panel acknowledged that the RECOVERY trial is assessing tocilizumab use in children and young people 1 year and over with paediatric inflammatory multisystem syndrome, and that tocilizumab is licensed for children and young people over 2 years. Therefore, tocilizumab may be considered for children and young people in a research setting.

Certainty of the Evidence

Very low

Because no evidence on tocilizumab in children was identified, the overall assessment of certainty is very low, and the recommendation includes a requirement for such use to be part of a clinical trial.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on patients' preferences and values. Despite the absence of evidence for tocilizumab in children, the serious consequences of paediatric inflammatory multisystem syndrome mean that tocilizumab is likely to be preferred over no treatment.

Resources

No important issues with the recommended alternative

No formal analysis of resource impact has been carried out. The panel commented that the availability of tocilizumab may differ across hospitals.

Equity

Important issues, or potential issues not investigated

The evidence identified does not include children and young people under 18 years. However, the RECOVERY trial is assessing tocilizumab use in children and young people 1 year and over with paediatric inflammatory multisystem syndrome, and tocilizumab is licensed for children and young people over 2 years. Therefore, tocilizumab may be considered for children and young people in a research setting.

Acceptability

Important issues, or potential issues not investigated

No qualitative evidence was identified that could be used to assess the acceptability of tocilizumab use. However, in the context of the COVID-19 pandemic, parents, children and clinicians would likely accept tocilizumab use for paediatric inflammatory multisystem syndrome as part of a clinical trial rather than having no treatment.

Feasibility

No important issues with the recommended alternative

The planned trial is expected to be carried out in a hospital setting. The panel considered this to be appropriate, and agreed that it reflects current practice for use and availability of tocilizumab.

Rationale

There is no evidence for tocilizumab use in children and young people with COVID-19. However, there is an ongoing UK trial (RECOVERY) including children and young people 1 year and over with severe COVID-19 or paediatric inflammatory multisystem syndrome. So, tocilizumab can be considered for children and young people in the context of a clinical trial.

7.5 Sarilumab

Info Box**Definition**

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the [Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'](#).

Conditional recommendation

Updated

Consider sarilumab for COVID-19 in adults in hospital if tocilizumab is unavailable for this condition or cannot be used. Use the same eligibility criteria as those for tocilizumab. That is, if all the following apply:

- they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
- they have not had another interleukin-6 inhibitor during this admission
- there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by sarilumab.

And they:

- need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
- are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

In October 2021, the marketing authorisations for sarilumab do not cover use in COVID-19. See [NICE's information on prescribing medicines for more about off-label and unlicensed use of medicines](#).

The recommended dosage for sarilumab is a single dose of 400 mg by intravenous infusion.

For sarilumab use in pregnancy, follow the [Royal College of Obstetrics and Gynaecology guidance on coronavirus \(COVID-19\) infection and pregnancy](#).

For full details of adverse events and contraindications, see the summaries of product characteristics.

See [NHS England's Interim Clinical Commissioning Policy on sarilumab for critically ill patients with COVID-19 pneumonia \(adults\)](#) for further information.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The evidence for sarilumab plus standard care for both reduction in mortality and adverse events is uncertain. Sarilumab plus standard care is statistically significantly more effective than standard care alone at reducing death at 60 days in adults with COVID-19 in hospital. However, the panel noted that this result came from 1 study with a moderate risk of bias. The evidence suggests that sarilumab plus standard care has little effect on reducing death at other timepoints compared with standard care alone.

The evidence also suggests that sarilumab does not increase the risk of adverse events of any severity.

The evidence shows that sarilumab plus standard care is statistically significantly more effective than standard care alone for a combined outcome of reducing death and reducing time on organ support.

The dosage for sarilumab is covered by [NHS England's Interim Clinical Commissioning Policy: Sarilumab for critically ill patients with COVID-19 pneumonia \(adults\)](#).

Details of special warnings and precautions for sarilumab use are in its summaries of product characteristics. It would also be beneficial to ensure that ongoing care providers in the community are informed about peoples' treatments when they are transferred from a hospital setting, so that they are aware of any potential long-term treatment effects.

Certainty of the Evidence

Moderate

The certainty of the evidence for all-cause mortality is moderate because of wide confidence intervals and missing data in 1 study.

The certainty of the evidence for adverse events is low to moderate because of wide confidence intervals and a lack of blinding in 1 study.

There is a moderate risk of bias for the combined outcome of death and days free from organ support because of a lack of blinding.

Preference and values

No substantial variability expected

The panel identified critical outcomes that would be important for decision making. These included all-cause mortality and serious adverse events. It is likely that these outcomes would also be of similar importance to people with COVID-19. In addition, less serious adverse events are likely to be of particular importance to people with COVID-19. This outcome was not as commonly reported in studies.

Resources

Important issues, or potential issues not investigated

No formal analysis of resource impact has been carried out. So, it is unknown whether sarilumab used early in COVID-19 disease might prevent later use of intensive care resources.

Equity

Important issues, or potential issues not investigated

Sarilumab has not been studied in people who are pregnant or breastfeeding, or in children and young people. The decision about whether someone who is pregnant meets the eligibility criteria should be considered by a multidisciplinary team that includes an obstetric specialist when possible. There are additional considerations for people who are breastfeeding or of childbearing potential who have sarilumab. This is outlined in the summaries of product characteristics.

No evidence has been identified that evaluated the efficacy of sarilumab in groups of people with other protected characteristics such as ethnicity.

Acceptability

No important issues with the recommended alternative

No evidence assessing the acceptability of sarilumab has been identified. However, in the context of the COVID-19 pandemic, it is likely that patients, and their families and clinicians would accept sarilumab use. This is because the benefits of reducing death and time on organ support seem to outweigh the risk of adverse events (if tocilizumab is unavailable for this condition or cannot be used).

Feasibility

No important issues with the recommended alternative

The trials were carried out in a hospital setting. The panel considered this to be appropriate and agreed that it reflects where sarilumab is used in current practice.

Rationale

The evidence review found that sarilumab plus standard care is statistically significantly more effective than standard care alone at reducing death at 60 days in adults with COVID-19 in hospital. The evidence also suggests that sarilumab plus standard care has little effect on reducing death at other timepoints and has little effect on adverse events of any severity.

There is sufficient evidence to recommend either tocilizumab or sarilumab. However, the evidence for tocilizumab is more certain. This is because there are more studies and more people in the studies for tocilizumab (7,603 people) than for sarilumab plus standard care (2,053 people).

Although evidence for the effectiveness of sarilumab is uncertain, it is an acceptable alternative if tocilizumab cannot be used or is unavailable. This is because, like tocilizumab, it is an interleukin-6 inhibitor and likely to have similar benefits and harms. The panel agreed that sarilumab should be offered if tocilizumab is not available for use in COVID-19. [Use the same eligibility criteria as those for tocilizumab.](#)

Clinical Question/ PICO

Population: People with COVID-19
Intervention: Sarilumab
Comparator: Standard care

Summary

There is uncertainty whether sarilumab is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?

This is an update to the March 2021 review. During this update, we have added an extra study (Sivapalasingam 2021) and updated a study with more recent data (REMAP-CAP 2021). Evidence now comes from three randomised trials that compared sarilumab with control in 2,053 adults hospitalised with severe or critical COVID-19 (REMAP-CAP 2021, Sivapalasingam 2021, Lescure 2021).

Publication status

Two studies are only available as preprints and therefore have not been peer reviewed: Sivapalasingam 2021 posted to medRxiv on 19 June 2021, and REMAP-CAP 2021 posted to medRxiv on 25 June 2021.

Study characteristics

One study (REMAP-CAP 2021) included people with suspected or confirmed COVID-19 who were admitted to an intensive care unit and were receiving respiratory or cardiovascular organ support. The other two studies (Sivapalasingam 2021, Lescure 2021) included people with confirmed COVID-19 who were admitted to hospital with 'severe' or 'critical' disease as defined in the studies. This meant that the patient population ranged from people needing supplemental oxygen through non-invasive and invasive ventilation to treatment in intensive care.

Mean or median age ranged from 59 to 63 years and women comprised 32 to 37% of patients across the studies. There was a higher proportion of patients with diabetes (37% vs 22%) and severe cardiovascular disease (12% vs 7%) in the standard care arm compared with the sarilumab arm in one trial (REMAP-CAP 2021) but baseline characteristics were more similar across the groups in the other two trials (Sivapalasingam 2021, Lescure 2021). The majority of patients in the three studies (80%) concomitantly received corticosteroids post-randomisation. Pregnant and breastfeeding women were ineligible.

Two studies (REMAP-CAP 2021, Sivapalasingam 2021) assessed sarilumab 200 mg and 400 mg doses and the other (Lescure 2021) assessed sarilumab 400 mg.

What are the main results?

Sarilumab plus standard care is statistically significantly more effective than standard care alone at reducing death at 60 days in adults with COVID-19 in hospital (RR 0.78 95% CI 0.64 to 0.94). However, there was no statistically significant difference in mortality with sarilumab plus standard care compared with standard care at other timepoints (29 days and 90 days). There is no difference in incidence of serious adverse events (RR 0.99 95% CI 0.85 to 1.15).

There does not appear to be any dose-dependent differences in effect on mortality or serious adverse events.

Our confidence in the results

Certainty of the evidence is moderate for all-cause mortality at 60 days because of serious risk of bias due to omitted mortality data, and moderate for serious adverse events due to serious imprecision (wide confidence intervals).

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Sarilumab	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality [All patients] Within 29 days of commencing treatment	Relative risk 0.88 (CI 95% 0.71 – 1.1) Based on data from 924 patients in 2 studies. ¹ (Randomized controlled)	311 per 1000 Difference:	274 per 1000 37 fewer per 1000 (CI 95% 90 fewer)	Moderate Due to serious imprecision ²	The pooled estimate of two studies found no statistically significant difference in mortality at 29 days with sarilumab compared with placebo in people with

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Sarilumab	Certainty of the Evidence (Quality of evidence)	Plain language summary
9 Critical			– 31 more)		COVID-19
All-cause mortality [All patients] Within 60 days of commencing treatment	Relative risk 0.78 (CI 95% 0.64 – 0.94) Based on data from 924 patients in 2 studies. ³ (Randomized controlled)	386 per 1000 Difference:	301 per 1000 85 fewer per 1000 (CI 95% 139 fewer – 23 fewer)	Moderate Because of serious risk of bias due to omitted mortality data ⁴	The pooled estimate of two studies found that mortality at 60 days was decreased with sarilumab compared with placebo in people with COVID-19
9 Critical					
All-cause mortality [All patients] Within 90 days of commencing treatment	Relative risk 0.89 (CI 95% 0.74 – 1.06) Based on data from 889 patients in 1 studies. (Randomized controlled)	370 per 1000 Difference:	329 per 1000 41 fewer per 1000 96 fewer – 22 more	Moderate Due to serious imprecision ⁵	One study found no statistically significant difference in mortality at 90 days with sarilumab compared with usual care in people with COVID-19
9 Critical					
Serious adverse events Day 60 to day 90	Relative risk 1.14 (CI 95% 0.75 – 1.73) Based on data from 2,053 patients in 3 studies. ⁶ (Randomized controlled)	184 per 1000 Difference:	210 per 1000 26 more per 1000 (CI 95% 46 fewer – 134 more)	Moderate Due to serious imprecision ⁷	The pooled estimate of three studies found no statistically significant difference in serious adverse events at day 60 to day 90
6 Important					
Adverse events Within 60 days of commencing treatment	Relative risk 1.01 (CI 95% 0.85 – 1.2) Based on data from 416 patients in 1 studies. (Randomized controlled)	667 per 1000 Difference:	674 per 1000 7 more per 1000 (CI 95% 100 fewer – 133 more)	Moderate Due to serious imprecision ⁸	One study found no statistically significant difference in adverse events at day 60 with sarilumab compared with placebo in people with COVID-19
6 Important					
Ordinal scale combining in-hospital mortality and days free of organ support ⁹ In-hospital mortality at 90 days and days free of organ support to day 21	Based on data from: 887 patients in 1 studies. (Randomized controlled)	Median adjusted odds ratio 1.50 (CI 95% 1.13 - 2.00)		Moderate Because of serious risk of bias due to lack of blinding ¹⁰	One study found that an ordinal scale combining 1.50 (99 favoured sarilumab compared with usual care
6 Important					
Days free of	Based on data from: 887	Sarilumab (median): 15 days (IQR 9 –		Moderate	One study found that

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Sarilumab	Certainty of the Evidence (Quality of evidence)	Plain language summary
organ support in survivors Days free of organ support in survivors to 21 days	patients in 1 studies. (Randomized controlled)	18); usual care: 13 days (IQR 4 – 17)		Because of serious risk of bias due to lack of blinding ¹¹	sarilumab had the greatest number of days free of organ support in survivors to 21 days, followed by tocilizumab, followed by usual care

1. Systematic review with included studies: [126], [127]. **Baseline/comparator:** Systematic review.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Due to serious imprecision.
3. Systematic review with included studies: [127], [126]. **Baseline/comparator:** Systematic review.
4. **Risk of Bias: serious.** Because of serious risk of bias due to omitted mortality data. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Due to serious imprecision.
6. Systematic review with included studies: [97], [127], [126]. **Baseline/comparator:** Systematic review.
7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
8. **Imprecision: serious.** Wide confidence intervals.
9. Odds ratio 1.50 (CI 95% 1.13 - 2.00)
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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7.6 Low molecular weight heparins

Info Box

For recommendations on the therapeutic use of low molecular weight heparins, see the [section on venous thromboembolism \(VTE\) prophylaxis](#).

7.7 Vitamin D supplementation

Info Box

For recommendations on vitamin D, see the [NICE COVID-19 rapid guideline on vitamin D](#).

7.8 Antibiotics

Info Box

Antibiotics should not be used for preventing or treating COVID-19 unless there is clinical suspicion of additional bacterial co-infection. See the [section on suspected or confirmed co-infection](#).

See also the recommendations on [azithromycin](#) and [doxycycline](#) in the section on therapeutics for COVID-19.

7.9 Azithromycin

Not recommended

Do not use azithromycin to treat COVID-19.

Evidence To Decision

<p>Benefits and harms</p> <p>The panel considered that the results from studies of azithromycin for moderate to critical COVID-19 in the hospital setting and mild to moderate COVID-19 in the community setting showed no meaningful benefit in any of the critical outcomes. They were also aware of the known cardiotoxicity risks associated with macrolide antibiotics. Considering this, the panel decided that the findings could not justify the use of azithromycin to treat COVID-19. They were also concerned that using azithromycin in this way may increase antimicrobial resistance and could have important antibiotic stewardship implications.</p>	<p>Small net benefit, or little difference between alternatives</p>
<p>Certainty of the Evidence</p> <p>For people in hospital, the certainty of the evidence for azithromycin for COVID-19 on all-cause mortality and invasive mechanical ventilation is moderate. This is because of serious imprecision with the confidence interval crossing the line of no effect. The certainty of the evidence for serious adverse events is low. This is because of serious risk of bias for some concerns around deviation from treatment protocols and serious imprecision for very few events.</p> <p>The certainty of the evidence for other important outcomes for azithromycin for COVID-19 in people in hospital ranges from low to very low. This is because of serious risk of bias (for some concerns around deviation from treatment protocols)</p>	<p>Low</p>

and serious imprecision (for very few events; only 1 study contributing to an outcome or the confidence interval crossing the line of no effect). The panel also considered that using hydroxychloroquine as standard care does not reflect current standard practice. Outcomes that were informed by evidence mainly from studies using hydroxychloroquine as standard care have therefore been downgraded for indirectness.

The certainty of the evidence ranges from moderate to low for the critical outcomes and very low for important outcomes for azithromycin for COVID-19 in the community setting. This is generally because of serious risk of bias (for concerns about missing data and incomplete reporting in 1 study, and lack of blinding for more subjective outcomes) and serious imprecision (for few events or only 1 study contributing to the outcome).

Preference and values

We expect few to want the intervention

The panel were not aware of any systematically collected data on peoples' preferences and values, but they identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for invasive mechanical ventilation and serious adverse events. It is likely that these outcomes would also be of similar importance to patients. In addition, other outcomes including less serious adverse events, discharge from hospital, duration of hospital stay and longer-term outcomes such as functional independence are likely to be of particular importance to patients. These outcomes were not as commonly reported in studies.

The panel inferred that, in view of the lack of meaningful benefit for people with COVID-19, the potential for harm and the risk of causing antimicrobial resistance, most would not choose azithromycin.

Resources

Important issues, or potential issues not investigated

Cost effectiveness was not assessed as part of the evidence review.

Equity

Important issues, or potential issues not investigated

The panel were not aware of any evidence for azithromycin use in children or pregnancy. However, because the overall recommendation is not to offer azithromycin to anyone, it is not expected to cause inequity among any subgroups.

Acceptability

Intervention is likely poorly accepted

The panel were not aware of any systematically collected evidence about acceptability. However, considering the important antibiotic stewardship implications and no evidence of effectiveness to treat COVID-19, use of azithromycin would not be acceptable unless there are other licensed indications for which its use remains appropriate.

Feasibility

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about feasibility.

Azithromycin is not used for treating COVID-19 in the UK, so the recommendation supports current practice.

Rationale

The evidence suggests that azithromycin is no better than standard care at reducing risk of death in people in hospital with COVID-19. Limited evidence also suggests that azithromycin does not reduce the risk of hospitalisation or death in people with COVID-19 in the community. There is no evidence for azithromycin use for COVID-19 in children. The panel did not think there were reasons to expect different results in this group, so agreed that the recommendation applies to all age groups. They also noted the risk of antimicrobial resistance with azithromycin.

Clinical Question/ PICO

Population:	People with COVID-19 (Hospitalised)
Intervention:	Azithromycin
Comparator:	Standard care

Summary

Compared to standard care, azithromycin is no better at reducing risk of death in people in hospital with COVID-19.

What is the evidence informing this conclusion?

Evidence comes from 4 randomised controlled trials that compared azithromycin with standard care in almost 10,000 adults hospitalised with COVID-19. (Furtado 2020; Sekhavati 2020; Cavalcanti 2020; Horby 2020). Most data are from the RECOVERY trial (Horby 2020) which included 7763 adults hospitalised with moderate-to-critical COVID-19.

Standard care within the trials varied. There were 3 trials that included hydroxychloroquine as part of standard care (Furtado 2020; Cavalcanti 2020; Sekhavati 2020). One trial also included lopinavir/ritonavir as part of standard care as well as hydroxychloroquine (Sekhavati 2020). The largest trial, which was conducted in the UK, did not include hydroxychloroquine as part of standard care (Horby 2020). The use of corticosteroids were permitted in 3 of the trials (Horby 2020; Furtado 2020; Cavalcanti 2020).

Due to the variability in standard care, subgroup analyses were conducted for key outcomes. These subgroup analyses were for hydroxychloroquine as standard care versus no hydroxychloroquine.

Publication status

All studies have been peer-reviewed.

Study characteristics

The mean age in the studies ranges between 50 and 67 years and the proportion of women ranged between 33 and 58%. The severity of COVID-19 across the studies was moderate-to-critical. One study only included people who required no oxygen or supplemental oxygen at baseline (Cavalcanti 2020). In the largest study, 76% of people were receiving supplemental oxygen at baseline. One study had 42% of people receiving oxygen at baseline and 49% people receiving mechanical ventilation at baseline.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 5 and 10 days. All studies used the oral route of administration for azithromycin. Two studies also used the IV route of administration (Furtado 2020 and Horby 2020) and 1 study used a nasogastric route as an option (Furtado 2020).

Children and pregnant women were excluded from the trials.

What are the main results?

Critical outcomes

All-cause mortality

Moderate quality evidence from 3 studies found no significant difference for all-cause mortality at 28-30 days with azithromycin compared with standard care for people who were hospitalised (5 fewer deaths per 1000 people [RR 0.98 95% CI 0.90 to 1.06; 8271 people in 3 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine was no different from the overall results.

Low quality evidence from 2 studies found no significant difference for all-cause mortality at 15 days with azithromycin compared with standard care for people who were hospitalised (0 fewer deaths per 1000 people [RR 1.00 95% CI 0.75 to 1.34; 728 people in 2 studies]).

Invasive mechanical ventilation

Moderate quality evidence from 1 study found no significant difference for requirement of IMV at 28-30 days with azithromycin compared with standard care for people who were hospitalised (8 fewer events per 1000 people [RR 0.92 95% CI 0.79 to 1.07; 7311 people in 1 study]).

Very low-quality evidence from 1 study found no significant difference for requirement of IMV at 15 days with azithromycin compared with standard care for people who were hospitalised (35 more events per 1000 people [RR 1.46 95% CI 0.73 to 2.92; 331 people in 1 study]).

Serious adverse events

Low quality evidence from 3 studies found no significant difference for serious adverse events with azithromycin

compared with standard care for people who were hospitalised (2 more events per 1000 people [RR 1.14 95% CI 0.91 – 1.43; 8640 people in 3 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine were no different from the overall results.

Important outcomes

Discharge from hospital

Low quality evidence from 2 studies found no significant difference for discharge from hospital at 29 days with azithromycin compared with standard care for people who were hospitalised (54 fewer events per 1000 people [RR 0.92 95% CI 0.71 to 1.19; 8161 people in 2 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine remained non-significant. However, there were differences in direction of effect (with hydroxychloroquine RR 0.78 95% CI 0.6 to 1.01; 397 people in 1 study; without hydroxychloroquine RR 1.02 95% CI 0.99 to 1.05; 7764 people in 1 study).

Very low-quality evidence from 2 studies found no significant difference for discharge from hospital at 15 days with azithromycin compared with standard care for people who were hospitalised (42 fewer events per 1000 people [RR 0.92 95% CI 0.82 to 1.02; 728 people in 2 studies]).

ICU admission

Low quality evidence from 1 study found no significant difference for ICU admission with azithromycin compared with standard care for people who were hospitalised (91 fewer events per 1000 people [RR 0.28 95% CI 0.06 to 1.29; 111 people in 1 study]).

Duration of hospital stay

Very low-quality evidence from 2 studies found no significant difference for duration of hospital stay with azithromycin compared with standard care for people who were hospitalised (MD -0.41 days 95% CI -2.42 to 1.59; 442 people in 2 studies).

Adverse events

Very low-quality evidence from 1 study found no significant difference for adverse events with azithromycin compared with standard care for people who were hospitalised (57 more events per 1000 people [RR 1.17 95% CI 0.91 to 1.50; 438 people in 1 study]).

Our confidence in the results

There were few concerns around risk of bias of studies. Although all studies were open label, it was not considered high risk of bias for the outcomes reported. This is because the objective outcomes such as all-cause mortality will not likely be affected by knowledge of intervention allocation. Other outcomes such as discharge from hospital could be affected by knowledge of intervention, but is probably unlikely in the pandemic situation. One study reported minor deviation from intervention protocols where some patients in the standard care arms also received azithromycin (Cavalcanti 2020). Outcomes that included this study were downgraded for risk of bias (serious adverse events, adverse events, duration of hospital stay and discharge from hospital).

The outcome discharge from hospital was downgraded for serious inconsistency due to statistical heterogeneity of I^2 of more than 50%.

Where an outcome was informed only by studies that had hydroxychloroquine as standard care, the outcome was downgraded due to serious indirectness. This is because hydroxychloroquine is not the current standard of care in the UK. This included 15-day all-cause mortality, 15-day invasive mechanical ventilation, 15-day discharge from hospital, ICU admission, duration of hospital stay and adverse events outcomes.

All outcomes were downgraded for imprecision due to the 95% CI crossing the line of no effect or if only 1 study informed the outcome.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Azithromycin	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality Within 28-30	Relative risk 0.98 (CI 95% 0.9 – 1.06) Based on data from	228 per 1000	223 per 1000	Moderate Due to serious imprecision ²	A pooled analysis of 3 studies found no significant difference for

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Azithromycin	Certainty of the Evidence (Quality of evidence)	Plain language summary
days of starting treatment 9 Critical	8,271 patients in 3 studies. ¹ (Randomized controlled)	Difference:	5 fewer per 1000 (CI 95% 23 fewer – 14 more)		all-cause mortality at 28-30 days with azithromycin compared with standard care for people who were hospitalised.
All-cause mortality Within 15 days of starting treatment 9 Critical	Relative risk 1 (CI 95% 0.75 – 1.34) Based on data from 728 patients in 2 studies. ³ (Randomized controlled)	175 per 1000 Difference:	175 per 1000 0 fewer per 1000 (CI 95% 44 fewer – 60 more)	Low Due to serious indirectness and due to serious imprecision ⁴	A pooled analysis of 2 studies found no significant difference for all-cause mortality at 15 days with azithromycin compared with standard care for people who were hospitalised
Invasive mechanical ventilation Within 28-30 days of starting treatment 9 Critical	Relative risk 0.92 (CI 95% 0.79 – 1.07) Based on data from 7,311 patients in 1 studies. ⁵ (Randomized controlled)	94 per 1000 Difference:	86 per 1000 8 fewer per 1000 (CI 95% 20 fewer – 7 more)	Moderate Due to serious imprecision ⁶	Evidence from 1 study found no significant difference for requirement of IMV at 28-30 days with azithromycin compared with standard care for people who were hospitalised
Invasive mechanical ventilation Within 15 days of starting treatment 9 Critical	Relative risk 1.46 (CI 95% 0.73 – 2.92) Based on data from 331 patients in 1 studies. ⁷ (Randomized controlled)	75 per 1000 Difference:	110 per 1000 35 more per 1000 (CI 95% 20 fewer – 144 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision ⁸	Evidence from 1 study found no significant difference for requirement of IMV at 15 days with azithromycin compared with standard care for people who were hospitalised
Serious adverse events During treatment 9 Critical	Relative risk 1.14 (CI 95% 0.91 – 1.43) Based on data from 8,640 patients in 3 studies. ⁹ (Randomized controlled)	14 per 1000 Difference:	16 per 1000 2 more per 1000 (CI 95% 1 fewer – 6 more)	Low Due to serious risk of bias and serious imprecision ¹⁰	A pooled analysis of 3 studies found no significant difference for serious adverse events with azithromycin compared with standard care for people who were hospitalised
Discharge from hospital Within 29 days of starting treatment 6 Important	Relative risk 0.92 (CI 95% 0.71 – 1.19) Based on data from 8,161 patients in 2 studies. ¹¹ (Randomized controlled)	671 per 1000 Difference:	617 per 1000 54 fewer per 1000 (CI 95% 195 fewer – 127 more)	Low Due to serious inconsistency, Due to serious imprecision ¹²	A pooled analysis of 2 studies found no significant difference for discharge from hospital at 29 days with azithromycin compared with standard care for people who were hospitalised
Discharge from hospital	Relative risk 0.92 (CI 95% 0.82 – 1.02) Based on data from 728	520 per 1000	478 per 1000	Very low Due to serious inconsistency,	A pooled analysis of 2 studies found no significant difference for

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Azithromycin	Certainty of the Evidence (Quality of evidence)	Plain language summary
Within 15 days of starting treatment 6 Important	patients in 2 studies. ¹³ (Randomized controlled)	Difference:	42 fewer per 1000 (CI 95% 94 fewer – 10 more)	serious risk of bias, serious indirectness and to serious imprecision ¹⁴	discharge from hospital at 15 days with azithromycin compared with standard care for people who were hospitalised
ICU admission During treatment 6 Important	Relative risk 0.28 (CI 95% 0.06 – 1.29) Based on data from 111 patients in 1 studies. ¹⁵ (Randomized controlled)	127 per 1000 Difference:	36 per 1000 91 fewer per 1000 (CI 95% 119 fewer – 37 more)	Low Due to serious imprecision and serious indirectness ¹⁶	Evidence from 1 study found no significant difference for ICU admission with azithromycin compared with standard care for people who were hospitalised
Adverse events During treatment 6 Important	Relative risk 1.17 (CI 95% 0.91 – 1.5) Based on data from 438 patients in 1 studies. ¹⁷ (Randomized controlled)	337 per 1000 Difference:	394 per 1000 57 more per 1000 (CI 95% 30 fewer – 169 more)	Very low Due to serious risk of bias, serious indirectness and serious imprecision ¹⁸	Evidence from 1 study found no significant difference for adverse events with azithromycin compared with standard care for people who were hospitalised
Duration of hospital stay	Measured by: Number of days Based on data from: 442 patients in 2 studies. ¹⁹ (Randomized controlled)	Difference:	MD 0.41 lower (CI 95% 2.42 lower – 1.59 higher)	Very low Due to serious risk of bias, serious indirectness and serious imprecision ²⁰	A pooled analysis of 2 studies found no significant difference for duration of hospital stay with azithromycin compared with standard care for people who were hospitalised

- Systematic review [1] with included studies: Furtado 2020 (COALITION II), Horby 2020 (RECOVERY), Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
- Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
- Systematic review [1] with included studies: Cavalcanti 2020, Furtado 2020 (COALITION II). **Baseline/comparator:** Control arm of reference used for intervention.
- Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. **Imprecision: serious.** due to 95% CI crosses the line of no effect, Only data from one study. **Publication bias: no serious.**
- Systematic review [1] with included studies: Horby 2020 (RECOVERY). **Baseline/comparator:** Control arm of reference used for intervention.
- Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
- Systematic review [1] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
- Risk of Bias: serious.** due to minor deviation from intervention. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. **Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
- Systematic review [1] with included studies: Horby 2020 (RECOVERY), Furtado 2020 (COALITION II), Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
- Risk of Bias: serious.** due to minor deviations from intervention. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** due to few events. **Publication bias: no serious.**
- Systematic review [1] with included studies: Horby 2020 (RECOVERY), Furtado 2020 (COALITION II). **Baseline/comparator:** Control arm of reference used for intervention.

12. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2 : 77 %.. **Indirectness: no serious.** **Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
13. Systematic review [1] with included studies: Cavalcanti 2020, Furtado 2020 (COALITION II). **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** due to minor deviations from intervention. **Inconsistency: no serious.** **Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** 95% CI crosses line of no effect, due to [reason]. **Publication bias: no serious.**
15. Systematic review [1] with included studies: Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious.** **Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
17. Systematic review [1] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** due to minor deviation from intervention. **Inconsistency: no serious.** **Indirectness: serious.** due to use of hydroxychloroquine as standard care.. **Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
19. Systematic review [1] with included studies: Sekhavati 2020, Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: serious.** due to minor deviation from intervention. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was high, with I^2 77%.. **Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** 95%CI crosses line of no effect. **Publication bias: no serious.**

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1. Azithromycin for COVID-19 internal meta-analysis.
2. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A., et al. : Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med 2020; [Journal](#)
3. Furtado RHM, Berwanger O., Fonseca HA, Corr?a TD, Ferraz LR, Lapa MG, et al. : Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet 2020;396(10256):959-967 [Journal](#)
4. Sekhavati E., Jafari F., SeyedAlinaghi S., Jamalimoghadamsiahkali S., Sadr S., Tabarestani M., et al. : Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial. Int J Antimicrob Agents 2020;56(4):106143 [Journal](#)
5. Horby : Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021; [Journal](#)

Clinical Question/ PICO

Population:	People with COVID-19 (Outpatients)
Intervention:	Azithromycin
Comparator:	Standard care

Summary

Compared to standard care, azithromycin probably does not reduce the risk of hospitalisation or death in people with COVID-19 managed in the community.

What is the evidence informing this conclusion?

Evidence comes from 3 randomised controlled trials that compared azithromycin with standard care in over 2000 adults with COVID-19 managed as outpatients or in the community (Omrani 2020; Butler 2021; Hinks 2021). Of these trials, 2 were conducted in the UK (Butler 2021; Hinks 2021).

Standard care within the trials varied. There was 1 trial that included hydroxychloroquine as part of standard care (Omrani 2020). The 2 trials conducted in the UK did not include hydroxychloroquine as part of standard care (Butler

2021; Hinks 2021). Concomitant corticosteroids use was reported in 1 trial (Hinks 2021).

Due to the variability in standard care, subgroup analyses were conducted for key outcomes. These subgroup analyses were for hydroxychloroquine as standard care versus no hydroxychloroquine.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 3 and 14 days. All studies used the oral route of administration for azithromycin.

There was 1 trial that was stopped early due to meeting its prespecified futility criterion (Butler 2021).

Publication status

There was 1 study which is currently only available as a pre-print which means it has not yet been peer-reviewed (Hinks 2021).

Study characteristics

The mean age in the studies ranges between 40 and 60 years and the proportion of women ranged between 48 and 57%. The PRINCIPLE trial recruited people who were 65 years or older or 50 years older with at least 1 comorbidity (Butler 2021). Whilst the Q-PROTECT trial planned to recruit women, over 98% were males (Omrani 2020). This was due female quarantine areas in Qatar often being inaccessible to male study physicians.

The severity of COVID-19 across the studies was mild to moderate but without the need for hospital admission.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 3 and 14 days.

Children and pregnant women were excluded from the trials.

What are the main results?

Critical outcomes

All-cause mortality

Low quality evidence from 3 studies found no significant difference for all-cause mortality with azithromycin compared with standard care for people who were managed as outpatients (0 fewer deaths per 1000 people [RR 1.01 95% CI 0.06 to 16.05; 1919 people in 3 studies]). There were no deaths reported in 2 of these studies (Omrani 2020 and Butler 2020). This meant that subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine was not possible.

Hospitalisation or death (composite)

Low quality evidence from 2 studies found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 people [RR 0.92 95% CI 0.59 to 1.43; 1615 people in 2 studies]).

Low quality evidence from 1 study found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients (13 fewer events per 1000 people [RR 0.82 95% CI 0.39 to 1.71; 422 people in 1 study]).

NIV/IMV or death (composite)

Moderate quality evidence from 1 study found no significant difference for NIV/IMV or death for azithromycin compared with standard care for people who were managed as outpatients (0 fewer events per 1000 [RR 1.01 95% CI 0.14 to 7.10; 292 people in 1 study]).

Invasive mechanical ventilation or ECMO

Low quality evidence from 1 study found no significant difference for IMV or ECMO for azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 [RR 0.50 95% CI 0.10 to 2.59; 1121 people in 1 study]).

Important outcomes

Virologic clearance

Low quality evidence from 1 study found no significant difference for virologic clearance at day 6 for azithromycin compared with standard care for people who were managed as outpatients (22 fewer events per 1000 [RR 0.83 95% CI 0.44 to 1.54; 301 people in 1 study]).

Low quality evidence from 1 study found no significant difference for virologic clearance at day 14 for azithromycin compared with standard care for people who were managed as outpatients (86 fewer per 1000 [RR 0.70 95% CI 0.46 to 1.05; 295 people in 1 study]).

Patient-reported clinical recovery

Patient reported recovery was defined as the first instance that a participant reported feeling recovered (Butler 2021).

Very low-quality evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients (38 more events per 1000 [RR 1.05 95% CI 0.99 to 1.11; 1323 people in 1 study]).

Very low-quality evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients (41 more events per 1000 people [RR 1.06 95% CI 0.94 to 1.20; 422 people in 1 study]).

Sustained clinical recovery

Sustained clinical recovery was defined as a participant who reported feeling recovered and subsequently remained well until 28 days after random assignment (Butler 2021).

Very low-quality evidence from 1 study found no significant difference for sustained clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients (26 fewer events per 1000 people [RR 0.96 95% CI 0.88 to 1.05; 1129 people in 1 study]).

ICU admission

Very low-quality evidence from 1 study found no significant difference for ICU admission at 28 days for azithromycin compared with standard care for people who were managed as outpatients (2 fewer ICU admissions per 1000 people [RR 0.76 95% CI 0.18 to 3.15; 1120 people in 1 study]).

Supplemental oxygen

Very low-quality evidence from 1 study found no significant difference for need for supplemental oxygen at 28 days for azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 people [RR 0.84 95% CI 0.38 to 1.85; 1122 people from 1 study]).

Our confidence in the results

Although all studies were open label, it was not considered high risk of bias for the mortality and invasive mechanical ventilation outcomes reported. However, outcomes which were considered more subjective were downgraded for risk of bias due to lack of blinding (patient-reported clinical recovery, sustained clinical recovery, ICU admission and supplemental oxygen). 1 study was unclear in how it accounted for missing data. Outcomes that included this study were downgraded for risk of bias (all-cause mortality, hospitalisation or death, invasive mechanical ventilation, patient-reported recovery, sustained clinical recovery, ICU admission and supplemental oxygen).

All outcomes were downgraded for imprecision due to the 95% CI crossing the line of no effect or if only 1 study informed the outcome.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Azithromycin	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality Within 28 days of starting treatment 9 Critical	Relative risk 1.01 (CI 95% 0.06 – 16.05) Based on data from 1,919 patients in 3 studies. ¹ (Randomized controlled)	1 per 1000 Difference:	1 per 1000 0 fewer per 1000 (CI 95% 1 fewer – 15 more)	Low Due to serious risk of bias and serious imprecision ²	A pooled analysis of 3 studies found no significant difference for all-cause mortality with azithromycin compared with standard care for people who were managed as outpatients.
Hospitalisation or death (composite) - All patients ³ Within 28 days of	Relative risk 0.92 (CI 95% 0.59 – 1.43) Based on data from 1,615 patients in 2 studies. ⁴ (Randomized controlled)	46 per 1000 Difference:	42 per 1000 4 fewer per 1000 (CI 95% 19 fewer	Low Due to serious risk of bias and serious imprecision ⁵	A pooled analysis of 2 studies found no significant difference for hospitalisation or death with azithromycin compared with standard

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Azithromycin	Certainty of the Evidence (Quality of evidence)	Plain language summary
starting treatment			– 20 more)		care for people who were managed as outpatients
9 Critical					
Hospitalisation or death (composite) - SARS-CoV-2 positive population ⁶ Within 28 days of starting treatment	Relative risk 0.82 (CI 95% 0.39 – 1.71) Based on data from 422 patients in 1 studies. ⁷ (Randomized controlled)	72 per 1000 Difference:	59 per 1000 13 fewer per 1000 (CI 95% 44 fewer – 51 more)	Low Due to serious risk of bias and serious imprecision ⁸	Evidence from 1 study found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who tested positive for SARS- CoV-2 and were managed as outpatients.
9 Critical					
NIV/IMV or death (composite) Within 28 days of starting treatment	Relative risk 1.01 (CI 95% 0.14 – 7.1) Based on data from 292 patients in 1 studies. ⁹ (Randomized controlled)	14 per 1000 Difference:	14 per 1000 0 fewer per 1000 (CI 95% 12 fewer – 85 more)	Moderate Due to serious imprecision ¹⁰	Evidence from 1 study found no significant difference for NIV/IMV or death for azithromycin compared with standard care for people who were managed as outpatients.
9 Critical					
Invasive mechanical ventilation or ECMO Within 28 days of starting treatment	Relative risk 0.5 (CI 95% 0.1 – 2.59) Based on data from 1,121 patients in 1 studies. ¹¹ (Randomized controlled)	8 per 1000 Difference:	4 per 1000 4 fewer per 1000 (CI 95% 7 fewer – 13 more)	Low Due to serious risk of bias and serious imprecision ¹²	Evidence from 1 study found no significant difference for IMV or ECMO for azithromycin compared with standard care for people who were managed as outpatients.
9 Critical					
Virologic clearance 6 days	Relative risk 0.83 (CI 95% 0.44 – 1.54) Based on data from 301 patients in 1 studies. ¹³ (Randomized controlled)	128 per 1000 Difference:	106 per 1000 22 fewer per 1000 (CI 95% 72 fewer – 69 more)	Low Due to serious indirectness and serious imprecision ¹⁴	Evidence from 1 study found no significant difference for virologic clearance at day 6 for azithromycin compared with standard care for people who were managed as outpatients.
6 Important					
Virologic clearance 14 days	Relative risk 0.7 (CI 95% 0.46 – 1.05) Based on data from 295 patients in 1 studies. ¹⁵ (Randomized controlled)	288 per 1000 Difference:	202 per 1000 86 fewer per 1000 (CI 95% 156 fewer – 14 more)	Low Due to serious indirectness and serious imprecision ¹⁶	Evidence from 1 study found no significant difference for virologic clearance at day 14 for azithromycin compared with standard care for people who were managed as outpatients.
6 Important					
Patient reported clinical recovery	Relative risk 1.05 (CI 95% 0.99 – 1.11) Based on data from	767 per 1000	805 per 1000	Very low Due to very	Evidence from 1 study found no significant difference for patient

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Azithromycin	Certainty of the Evidence (Quality of evidence)	Plain language summary
- All patients Within 28 days of starting treatment 6 Important	1,323 patients in 1 studies. ¹⁷ (Randomized controlled)	Difference:	38 more per 1000 (CI 95% 8 fewer — 84 more)	serious risk of bias and serious imprecision ¹⁸	reported clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients.
Patient reported clinical recovery - SARS-CoV-2 positive population Within 28 days of starting treatment 6 Important	Relative risk 1.06 (CI 95% 0.94 — 1.2) Based on data from 422 patients in 1 studies. ¹⁹ (Randomized controlled)	691 per 1000 Difference:	732 per 1000 41 more per 1000 (CI 95% 41 fewer — 138 more)	Very low Due to very serious risk of bias and serious imprecision ²⁰	Evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients.
Sustained clinical recovery Within 28 days of starting treatment 6 Important	Relative risk 0.96 (CI 95% 0.88 — 1.05) Based on data from 1,129 patients in 1 studies. ²¹ (Randomized controlled)	658 per 1000 Difference:	632 per 1000 26 fewer per 1000 (CI 95% 79 fewer — 33 more)	Very low Due to very serious risk of bias and serious imprecision ²²	Evidence from 1 study found no significant difference for sustained clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients.
ICU admission Within 28 days of starting treatment 6 Important	Relative risk 0.76 (CI 95% 0.18 — 3.15) Based on data from 1,120 patients in 1 studies. ²³ (Randomized controlled)	8 per 1000 Difference:	6 per 1000 2 fewer per 1000 (CI 95% 7 fewer — 17 more)	Very low Due to very serious risk of bias and serious imprecision ²⁴	Evidence from 1 study found no significant difference for ICU admission at 28 days for azithromycin compared with standard care for people who were managed as outpatients.
Supplemental oxygen Within 28 days of starting treatment 6 Important	Relative risk 0.84 (CI 95% 0.38 — 1.85) Based on data from 1,122 patients in 1 studies. ²⁵ (Randomized controlled)	24 per 1000 Difference:	20 per 1000 4 fewer per 1000 (CI 95% 15 fewer — 20 more)	Very low Due to very serious risk of bias and serious imprecision ²⁶	Evidence from 1 study found no significant difference for need for supplemental oxygen at 28 days for azithromycin compared with standard care for people who were managed as outpatients

1. Systematic review [1] with included studies: Omrani 2020, Hinks 2021, Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Very few events. **Publication bias: no serious.**
3. Population includes people who tested negative for SARS-CoV-19 during treatment
4. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE), Hinks 2021. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

6. Subpopulation who testing positive for SARS-CoV-19
7. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses line of no effect. **Publication bias: no serious.**
9. Systematic review [1] with included studies: Hinks 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
11. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
13. Systematic review [1] with included studies: Omrani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
15. Systematic review [1] with included studies: Omrani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** due to [reason]. **Publication bias: no serious.**
17. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: very serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
19. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
21. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
23. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
24. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
25. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
26. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**

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1. Azithromycin for COVID-19 internal meta-analysis.

6. Omrani AS, Pathan SA, Thomas SA, Harris TRE, Coyle PV, Thomas CE, et al. : Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. *EClinicalMedicine* 2020;29 100645 [Journal](#)

7. Butler : Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* (London,

England) 397(10279):1063-1074 [Journal](#)

8. Hinks TS CLKRE : A randomised clinical trial of azithromycin versus standard care in ambulatory COVID-19 ? the ATOMIC2 trial. medRxiv 2021;

7.10 Budesonide (inhaled)

Only in research settings

New

Only use budesonide to treat COVID-19 as part of a clinical trial.

People already on budesonide for conditions other than COVID-19 should continue treatment if they test positive for COVID-19.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel considered that the clinical evidence suggests there is no statistically significant difference for the outcomes of hospitalisation and death, or need for mechanical ventilation in people having inhaled budesonide and usual care compared with usual care alone. They considered that inhaled budesonide statistically significantly reduces the need for oxygen administration compared with usual care. The panel acknowledged that the event rates for these outcomes were low. This may be explained in part by the fact that the population had mild COVID-19 that was managed in the community. The panel noted that the thresholds for starting oxygen therapy were not reported in the trials.

Time to first reported recovery (patient reported) and time to sustained recovery was statistically significantly reduced with inhaled budesonide compared with usual care. However, the panel acknowledged that corticosteroids can potentially affect wellbeing without affecting the COVID-19 disease process. There was a statistically significant reduction in the number of people who had COVID-19-related urgent care visits. There was no statistically significant difference in serious adverse events for budesonide compared with usual care. The panel also discussed that non-serious adverse events were not reported in the studies. However, they acknowledged that the side-effect profile of budesonide is well known.

Certainty of the Evidence

Moderate

Most of the evidence was rated as low to moderate in quality. Outcomes that were self-reported were downgraded because of high risk of bias. When 95% confidence intervals crossed the line of no effect, the outcome was downgraded for imprecision. The outcome for COVID-19-related urgent-care visits was downgraded because of indirectness. It was not possible to determine from the data what the nature of the visits were because it included hospitalisations as well as emergency department attendance. These can lead to different outcomes for people with COVID-19.

The panel discussed the limitations of the trials and noted that the STOIC trial was a small study with very few events. They also noted the trial was stopped early as a result of an independent statistical review

Risk of bias was rated as 'low' or 'some concerns' for all outcomes in the studies. Both trials included were open-label studies. So, the lack of blinding could have introduced bias to the more subjective outcomes such as self-reported recovery, resolution of symptoms or sustained recovery. This is because people in the trials would have been aware of the treatment they were having.

The panel discussed that the PRINCIPLE trial had a restricted population of mainly older adults and had concerns about the applicability of the trial to younger people with COVID-19. The panel noted that inhalers can be difficult to use for people

unfamiliar with the devices, and so the amount of budesonide inhaled may be variable, potentially affecting the results.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences and values, but they identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for invasive mechanical ventilation, time to recovery and serious adverse events. It is likely that these outcomes would also be of similar importance to patients. In addition, other outcomes, including less serious adverse events and longer-term outcomes such as functional independence, are likely to be of particular importance to patients. These outcomes were not reported in studies.

Resources

Important issues, or potential issues not investigated

Cost effectiveness was not assessed as part of the evidence review.

Equity

Important issues, or potential issues not investigated

The panel discussed that not everyone will be able to use an inhaler, which could cause equity issues should inhaled budesonide be recommended for treating COVID-19 in the future.

Acceptability

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about acceptability.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility.

Inhaled budesonide is not routinely used for treating COVID-19 in the UK, so the recommendation supports current practice.

Rationale

Trial evidence suggests some benefit with inhaled budesonide in reducing how long it takes to recover from COVID-19. However, this evidence is limited because it comes from only 2 trials, 1 of which was very small and stopped early. Also, the population in the trials was mainly older people, which limits its generalisability to other age groups. The panel concluded that more research is needed to address these issues, and that inhaled budesonide should therefore only be used as part of a clinical trial.

Clinical Question/ PICO

Population: Non-hospitalised adults with COVID-19
Intervention: Inhaled budesonide
Comparator: Standard care, standard care plus placebo, or placebo

Summary

What is the evidence informing this recommendation?

The evidence review has been developed using [NICE interim process and methods for guidelines developed in response to health and social care emergencies](#).

Two studies identified from the search are included in this evidence review. The 2 randomised trials compared inhaled budesonide with usual care in 3217 non-hospitalised people with mild COVID-19 (Ramakrishnan 2021 [STOIC trial] and Yu 2021 [PRINCIPLE trial]).

Study characteristics

Both studies used a dosage of 800 micrograms twice daily (1600 micrograms total daily dose) of inhaled budesonide. The included studies compared inhaled budesonide to usual care which was based on advice from the UK National Health Service (NHS). The mean ages in the STOIC trial were 44 (range 19-71) years in the budesonide group and 46 (19-79) years in the usual care group. The PRINCIPLE trial restricted enrolment to a higher risk population with 39% of the participants aged between 50 and 64 years and 61% were aged over 64 years. The proportion of women ranged from 52% to 58%. Both studies were conducted in a non-hospital setting.

What are the main results?

Efficacy

In non-hospitalised adults with COVID-19, there were no statistically significant differences for reduction of hospitalisation or death, need for mechanical ventilation, ICU admission, symptom-related outcomes or hospital assessment without admission (Yu 2021) but there was a statistically significant difference favouring inhaled budesonide for reducing need for oxygen administration, time to first reported recovery, sustained recovery (Yu 2021) and the number of COVID-19-related urgent care visits, including emergency department assessment or hospitalisation (Ramakrishnan 2021).

Safety

There was no statistically significant difference in serious adverse events (Yu 2021).

Subgroup analysis

There was insufficient detail to accurately assess subgroups of interest.

Limitations of the evidence

There were some differences in how the included studies were designed which meant that meta-analysis was not appropriate. The population inclusion criteria of the STOIC trial (Ramakrishnan 2021) was broad (symptomatic adults aged ≥ 18 years) whereas the PRINCIPLE trial (Yu 2021 Academic in confidence) was restricted to adults that were at higher risk of complications with COVID-19 (≥ 65 years or ≥ 50 years with comorbidities). This restricted population in the PRINCIPLE trial will mean that the data may not be generalisable to younger adults with or without comorbidities.

The STOIC trial was terminated early after independent statistical review. This was because recruitment was reduced after a second national lockdown came into effect in England and implementation of the COVID-19 vaccine had started. Although the STOIC trial was terminated early and did not reach its target sample size, independent statistical review concluded that the addition of more participants would not have changed the result. However, this means that it was a very small trial with few events which may limit impact on decision-making.

Risk of bias for all outcomes was rated as 'low' or 'some concerns'. Both studies were open-label studies whereby lack of blinding could introduce bias to the more subjective outcomes. Lack of blinding is less likely to introduce bias to objective outcomes such as hospitalisation or death.

All included studies were in adults, so it is not possible to say what the efficacy or safety of inhaled budesonide for treating COVID-19 is in children or young people.

Our confidence in the results

The majority of the evidence was rated as low to moderate quality. Outcomes that were self-reported were downgraded due to high risk of bias. Where 95% confidence intervals crossed the line of no effect, the outcome was downgraded for imprecision. The outcome for COVID-19 related urgent-care visits was downgraded due to indirectness as it was not possible to determine from the data what the nature of the visits were as it included hospitalisations as well as emergency department attendance which can lead to different outcomes for patients.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Inhaled budesonide	Certainty of the Evidence (Quality of evidence)	Plain language summary
Hospitalisation or death related to COVID-19 [SARS-CoV-2 positive only] Within 28 days of starting treatment 9 Critical	Odds Ratio 0.75 (CI 95% 0.55 – 1.03) Based on data from 1,856 patients in 1 studies. (Randomized controlled)			Moderate Due to serious imprecision ¹	1 study found a non- statistically significant reduction in hospitalisation or death with inhaled budesonide compared with usual care.
Hospitalisation or death related to COVID-19 [whole study population] Within 28 days of starting treatment 9 Critical	Odds Ratio 0.78 (CI 95% 0.57 – 1.04) Based on data from 2,848 patients in 1 studies. (Randomized controlled)			Moderate Due to serious imprecision ²	1 study found a non- statistically significant reduction in hospitalisation or death with inhaled budesonide compared with usual care.
Mechanical ventilation [SARS-CoV-2 positive only] Within 28 days of starting treatment 9 Critical	Relative risk 0.94 (CI 95% 0.44 – 1.98) Based on data from 1,560 patients in 1 studies. ³			Moderate Due to serious imprecision ⁴	1 study found no statistically significant difference in mechanical ventilation with inhaled budesonide compared with usual care
Serious adverse events Within 28 days of starting treatment 9 Critical	Relative risk 1.36 (CI 95% 0.27 – 6.71) Based on data from 1,856 patients in 1 studies. ⁵ (Randomized controlled)			Low Due to very serious imprecision ⁶	1 study found no statistically significant difference in serious adverse events with inhaled budesonide compared with usual care
Time to first reported recovery [SARS- CoV-2 positive only] 9 Critical	Hazard Ratio 1.21 (CI 95% 1.08 – 1.36) Based on data from 1,856 patients in 1 studies. (Randomized controlled)			Moderate Due to serious risk of bias ⁷	1 study found a statistically significant decrease in time to first reported recovery with inhaled budesonide compared with usual care.
Time to first reported recovery [whole study population]	Hazard Ratio 1.18 (CI 95% 1.07 – 1.3) Based on data from 2,848 patients in 1 studies. (Randomized controlled)			Moderate Due to serious risk of bias ⁸	1 study found a statistically significant decrease in time to first reported recovery with inhaled budesonide compared with usual

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Inhaled budesonide	Certainty of the Evidence (Quality of evidence)	Plain language summary
9 Critical					care.
COVID-19-related urgent care visits, including emergency department assessment or hospitalisation [whole study population] Within 14 days of starting treatment	Relative risk 0.18 (CI 95% 0.04 – 0.79) Based on data from 146 patients in 1 studies. ⁹ (Randomized controlled)	151 per 1000 Difference:	27 per 1000 124 fewer per 1000 (CI 95% 145 fewer – 32 fewer)	Moderate Due to serious indirectness ¹⁰	1 study found a statistically significant reduction in people who require urgent care including hospitalisation with inhaled budesonide compared with usual care.
9 Critical					
COVID-19-related urgent care visits, including emergency department assessment or hospitalisation [SARs-CoV-2 positive only] Within 14 days of starting treatment	Relative risk 0.12 (CI 95% 0.02 – 0.96) Based on data from 131 patients in 1 studies. ¹¹ (Randomized controlled)	123 per 1000 Difference:	15 per 1000 108 fewer per 1000 (CI 95% 121 fewer – 5 fewer)	Moderate Due to serious indirectness ¹²	1 study found a statistically significant reduction in people who require urgent care including hospitalisation with inhaled budesonide compared with usual care.
9 Critical					
Hospital assessment without admission [SARS-CoV-2 positive only] Within 28 days of starting treatment	Relative risk 1.01 (CI 95% 0.57 – 1.82) Based on data from 1,583 patients in 1 studies. ¹³ (Randomized controlled)	28 per 1000 Difference:	28 per 1000 0 fewer per 1000 (CI 95% 12 fewer – 23 more)	Low Due to serious imprecision, Due to serious risk of bias ¹⁴	1 study found no statistically significant difference in hospital assessment without admission with inhaled budesonide compared with usual care.
9 Critical					
ICU admission [SARS-CoV-2 positive only] Within 28 days of starting treatment	Relative risk 0.48 (CI 95% 0.23 – 1.01) Based on data from 1,550 patients in 1 studies. ¹⁵ (Randomized controlled)	27 per 1000 Difference:	13 per 1000 14 fewer per 1000 (CI 95% 21 fewer – 0 fewer)	Moderate Due to serious imprecision ¹⁶	1 study found a non-statistically significant reduction in ICU admission with inhaled budesonide compared with usual care.
6 Important					

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Inhaled budesonide	Certainty of the Evidence (Quality of evidence)	Plain language summary
Oxygen administration [SARS-CoV-2 positive only] Within 28 days of starting treatment 6 Important	Relative risk 0.69 (CI 95% 0.49 – 0.98) Based on data from 1,559 patients in 1 studies. ¹⁷ (Randomized controlled)	93 per 1000 Difference:	64 per 1000 29 fewer per 1000 (CI 95% 47 fewer – 2 fewer)	High	1 study found a statistically significant reduction in oxygen administration with inhaled budesonide compared with usual care
Sustained recovery [SARS-CoV-2 positive only] Within 28 days of starting treatment 6 Important	Relative risk 1.2 (CI 95% 1.1 – 1.32) Based on data from 1,586 patients in 1 studies. ¹⁸ (Randomized controlled)	488 per 1000 Difference:	586 per 1000 98 more per 1000 (CI 95% 49 more – 156 more)	Moderate Due to serious risk of bias ¹⁹	1 study found a statistically significant improvement in sustained recovery with inhaled budesonide compared with usual care.
Time to sustained recovery [SARS-CoV-2 positive only] 4 Important	Hazard Ratio 1.39 (CI 95% 1.21 – 1.59) Based on data from 1,586 patients in 1 studies. (Randomized controlled)			Moderate Due to serious risk of bias ²⁰	1 study found a statistically significant decrease in time to sustained recovery with inhaled budesonide compared with usual care.
Initial reduction of severity of symptoms [SARS-CoV-2 positive only] Within 28 days of starting treatment 6 Important	Relative risk 1.03 (CI 95% 0.99 – 1.08) Based on data from 1,583 patients in 1 studies. ²¹ (Randomized controlled)	816 per 1000 Difference:	840 per 1000 24 more per 1000 (CI 95% 8 fewer – 65 more)	Low Due to serious risk of bias, Due to serious imprecision ²²	1 study found no statistically significant difference in initial severity of symptoms with inhaled budesonide compared with usual care.
Time to initial reduction of severity of symptoms [SARS-CoV-2 positive only] 6 Important	Hazard Ratio 1.19 (CI 95% 1.07 – 1.32) Based on data from 1,583 patients in 1 studies. (Randomized controlled)			Moderate Due to serious risk of bias ²³	1 study found a statistically significant decrease in time to initial reduction of severity of symptoms with inhaled budesonide compared with usual care.
Symptom resolution (All patients) Within 14 days of starting treatment	Relative risk 1.15 (CI 95% 0.95 – 1.41) Based on data from 142 patients in 1 studies. ²⁴ (Randomized controlled)	681 per 1000 Difference:	783 per 1000 102 more per 1000	Low Due to serious risk of bias, Due to serious imprecision ²⁵	1 study found no statistically significant difference in symptom resolution with inhaled budesonide compared with usual care.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Inhaled budesonide	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important			(CI 95% 34 fewer – 279 more)		
Alleviation of all of symptoms [SARS-CoV-2 positive only] Within 28 days of starting treatment	Relative risk 0.99 (CI 95% 0.96 – 1.02) Based on data from 1,433 patients in 1 studies. ²⁶ (Randomized controlled)	910 per 1000 Difference:	901 per 1000 9 fewer per 1000 (CI 95% 36 fewer – 18 more)	Low Due to serious risk of bias, Due to serious imprecision ²⁷	1 study found no statistically significant difference in alleviation of all symptoms with inhaled budesonide compared with usual care.
6 Important					
Time to alleviation of all symptoms [SARS-CoV-2 positive only]	Hazard Ratio 1.07 (CI 95% 0.96 – 1.19) Based on data from 1,433 patients in 1 studies. (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision ²⁸	1 study found no statistically significant difference in time to alleviation of all symptoms with inhaled budesonide compared with usual care.
6 Important					
Time to recovery	Measured by: Days Lower better Based on data from: 139 patients in 1 studies. ²⁹ (Randomized controlled)	Difference:	MD 4 lower (CI 95% 6.22 lower – 1.78 lower)	Moderate Due to serious risk of bias ³⁰	1 study found a statistically significant reduction in time to recovery with inhaled budesonide compared with usual care.

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect.
Publication bias: no serious.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect.
Publication bias: no serious.
3. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect.
Publication bias: no serious.
5. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** 95% CI crosses the line of no effect and very few events. **Publication bias: no serious.**
7. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
8. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
9. Systematic review [92] with included studies: STOIC 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate, not patient-important). **Imprecision: no serious. Publication bias: no serious.**
11. Systematic review [92] with included studies: STOIC 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Inconsistency: no serious. Indirectness: serious.** Differences between the outcomes of interest and those reported (e.g

short-term/surrogate, not patient-important). **Imprecision: no serious. Publication bias: no serious.**

13. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.

14. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

15. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.

16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

17. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.

18. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.

19. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

20. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

21. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.

22. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

23. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

24. Systematic review [92] with included studies: STOIC 2021. **Baseline/comparator:** Control arm of reference used for intervention.

25. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

26. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.

27. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

28. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

29. Systematic review [92] with included studies: STOIC 2021. **Baseline/comparator:** Control arm of reference used for intervention.

30. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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95. Yu L-M, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. : Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet (London, England)* 2021;398(10303):843-855 [Pubmed](#) [Journal](#)

7.11 Colchicine

Not recommended

Do not offer colchicine to people in hospital to treat COVID-19.

NICE is aware that there is newly published evidence on colchicine from the RECOVERY trial and this is being reviewed.

Evidence To Decision

Benefits and harms

Important harms

The panel considered that the results from studies of colchicine for COVID-19 in hospitals showed no convincing evidence of effect on all-cause mortality or mechanical ventilation. They were also aware that the colchicine arm of the [RECOVERY trial](#) stopped recruitment because of futility – that is, no effect on mortality was seen for people having colchicine and recruitment of more people into the trial was not expected to change this finding. This was reported in a press release in March 2021. When the full results are published, they will be considered in the evidence review.

Known adverse effects such as diarrhoea appeared to have been under-reported in the identified evidence. The panel noted that colchicine commonly caused diarrhoea, which can lead to potassium deficiency (hypokalaemia). They advised that, because of the adverse effects, colchicine tends to be used (for the treatment of gout) only for 3 to 4 days.

Certainty of the Evidence

Very low

The overall certainty of the evidence for colchicine to treat COVID-19 in people in hospital is very low because of risk of bias and imprecision. There was a serious risk of bias for most outcomes because allocation concealment and blinding (of people in the studies or the outcome assessors) were inadequately reported. There was serious or very serious imprecision for all outcomes, generally because of low numbers of people in the studies, few outcome events or wide confidence intervals.

The panel were concerned that the studies did not represent current practice in the UK. Only 1 of the 3 hospital-based studies reported that people having colchicine also had corticosteroids. The panel noted that corticosteroids are part of standard care for COVID-19. They additionally noted that, in the included studies, standard care included hydroxychloroquine and azithromycin, which are not part of standard care in the UK.

Preference and values

We expect few to want the intervention

The panel were not aware of any systematically collected data on peoples' preferences and values.

The panel thought that people would not want to take a treatment with no known benefits but well-established side effects such as diarrhoea.

Resources

No important issues with the recommended alternative

Cost effectiveness was not assessed as part of the evidence review.

Colchicine costs from £1.73 for 28 tablets ([BNF](#), April 2021). The panel therefore expected a negligible effect on resources.

Equity

No important issues with the recommended alternative

Colchicine should not be used in pregnancy and no studies in children were identified. However, because the overall recommendation is not to offer colchicine to anyone, it is not expected to cause inequity among any subgroups.

Acceptability

Intervention is likely poorly accepted

The panel were not aware of any systematically collected evidence about acceptability.

Colchicine is not licensed in the UK for treating COVID-19. The panel noted that its side effects are unlikely to be acceptable to patients or prescribers, especially diarrhoea and hypokalaemia. The panel noted that diarrhoea is particularly concerning in older people because frequent toilet visits and dehydration could be a risk factor for falls. They also noted that avoidable diarrhoea would not be acceptable in the intensive care setting.

Feasibility

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about feasibility.

Colchicine is not used for treating COVID-19 in the UK, so the recommendation supports current practice.

Rationale

The evidence from trials of colchicine to treat COVID-19 in adults in hospital suggests no beneficial effect on all-cause mortality and the need for mechanical ventilation. There is no evidence in this setting for children or young people. Therefore, colchicine should not be used to treat COVID-19 in people in hospital of any age.

Clinical Question/ PICO

Population: People with COVID-19 in hospital
Intervention: Colchicine
Comparator: Placebo or standard care

Summary

There remains uncertainty whether colchicine is more effective than placebo or standard care and acceptably safe in treating hospitalised patients with COVID-19.

What is the evidence informing this conclusion?

Evidence comes from 3 randomised trials that compared colchicine with placebo or standard care in 277 adults admitted to hospital with COVID-19 (Deftereos et al. 2020 [46]; Lopes et al. 2021 [47]; Salehzadeh et al. 2020 [48]).

The colchicine arm of the [RECOVERY trial](#) stopped recruitment because of futility of the intervention – that is, no effect on mortality was seen for existing participants and recruitment of further participants was not expected to change this finding. This was reported in a press release in March 2021. We are aware that a preprint report has now published and this is being reviewed.

Publication status

The study by Salehzadeh et al. (2020) [48] was only available as a preprint and has therefore not been peer reviewed.

Study characteristics

The median age ranged from 55 to 64 years and the proportion of women ranged from 42% to 59%. The severity of COVID-19 was not clearly reported across studies. In the study by Deftereos 2020 [46], an arterial oxygen partial pressure of lower than 95 mm Hg on room air was a key inclusion criterion. Lopes et al. (2021) [47] specified moderate to severe COVID-19 as an inclusion criterion but did not report how many patients of each category of severity were recruited. Salehzadeh et al. (2020) [48] did not define disease severity other than specifying COVID-19 with confirmed lung involvement.

The dosage of colchicine differed across the studies. Deftereos et al. (2020) [46] and Lopes et al. (2021) [47] used a higher initial dose (from 1 mg daily to 2 mg daily) for between 1 and 5 days before switching to a lower maintenance dose. The daily dose in the maintenance phase was 1 mg (Deftereos et al. 2020 [46]; Lopes et al. 2021 [47]; Salehzadeh et al. 2020 [48]). Duration of treatment ranged from 6 days to 3 weeks across the studies.

Most of the participants also received hydroxychloroquine (or chloroquine) and azithromycin as part of standard care (Deftereos et al. 2020 [46]; Lopes et al. 2021 [47]; Salehzadeh et al. 2020 [48]). Deftereos et al. (2020) [46] compared colchicine with standard care which included using hydroxychloroquine (or chloroquine) in 98% of participants and azithromycin in 92% of participants.

Follow-up ranged from 2 to 3 weeks; however Lopes et al. (2021) [47] did not clearly report the duration of follow-up.

Pregnant and breastfeeding women were excluded from all studies. No children were included.

What are the main results?

For the critical outcomes of mortality and need for mechanical ventilation, there was no statistically significant effect within 21 to 28 days of starting colchicine treatment compared with placebo or standard care. The certainty of evidence for these outcomes was very low. There were too few events to determine whether colchicine is effective in hospitalised patients with COVID-19, and the confidence interval includes the possibility of benefit or harm.

For the important outcomes:

- colchicine statistically significantly increased the proportion of people who are discharged from hospital after 10 days compared with placebo or standard care, but this finding was from very low certainty evidence.
- a statistically significant increase in the number of adverse events were seen at the end of follow-up with colchicine compared with placebo or standard care.
- no serious adverse events were reported in either group in one study (Deftereos et al. 2020 [46]); therefore, no calculation of relative effects was possible so this outcome is not shown in the evidence profile.
- for clinical progression (defined as an increase of 2 grades on a 7-grade scale) and ICU admission, at 21 days after starting treatment there were no statistically significant effects seen for colchicine compared with placebo or standard care.
- for duration of hospital stay, the report included the mean for each group but not the standard deviation therefore it was not possible to calculate the relative effect and confidence intervals for this outcome. The duration was 1.84 days shorter with colchicine compared with placebo or standard care, but this data was from only 1 study (Salehzadeh et al. 2020 [48]) rated as at very serious risk of bias and should be interpreted with caution.
- for discontinuation due to adverse events, 2 discontinuations were reported in the colchicine group compared with 0 in the standard care group and it was not possible to calculate the absolute effect estimates, resulting in a value of 0 events in both groups (relative risk 4.55, 95% CI 0.22 to 92.62, n=177, 2 studies (Salehzadeh et al. 2020 [48]; Lopes et al. 2021 [47])). This outcome is not shown in the evidence profile, because of the incomplete data for the absolute effects.

Adverse event reporting varied across the studies. Salehzadeh et al. (2020) [48] did not report on adverse event rates. Deftereos et al. (2020) [46] reported 1 case of moderate thrombocytopenia in the control group and 1 case of moderate diarrhoea in the colchicine group. In Lopes et al. (2021) [47], new or worsened diarrhoea was more frequent with colchicine compared with placebo (17% vs 6%). However, this difference was not statistically significant. No statistically significant differences between the groups were seen for aspartate transaminase or alanine aminotransferase elevations, nausea or vomiting, abdominal pain, hospital-acquired pneumonia, arrhythmia, or QT interval. The duration of follow-up for adverse events was not always reported clearly but appears to be a maximum of 3 weeks after starting treatment.

Our confidence in the results

The certainty of evidence was rated as very low for the critical outcomes of all-cause mortality and mechanical ventilation because of few events and wide confidence intervals.

All other outcomes were rated as very low certainty evidence, because of serious risk of bias and very serious inconsistency. For all studies, allocation concealment and assessor blinding were at unclear or high risk of bias. Participant blinding was a concern in 2 of 3 studies. Concerns around inconsistency included wide confidence intervals, and low numbers of both participants and outcome events.

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Colchicine	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality Within 21-28 days of starting treatment 9 Critical	Relative risk 0.22 (CI 95% 0.04 – 1.25) Based on data from 177 patients in 2 studies. ¹ (Randomized controlled)	70 per 1000 Difference:	15 per 1000 55 fewer per 1000 (CI 95% 67 fewer – 18 more)	Very low Due to serious risk of bias, Due to very serious imprecision ²	2 studies found no statistically significant difference in all-cause mortality at days 21 to 28 with colchicine compared with placebo or standard care.

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Colchicine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mechanical ventilation Within 21-28 days of starting treatment 9 Critical	Relative risk 0.15 (CI 95% 0.02 – 1.22) Based on data from 105 patients in 1 studies. ³ (Randomized controlled)	120 per 1000 Difference:	18 per 1000 102 fewer per 1000 (CI 95% 118 fewer – 26 more)	Very low Due to serious risk of bias, Due to very serious imprecision ⁴	1 study found no statistically significant difference in mechanical ventilation at days 21 to 28 with colchicine compared with standard care.
Adverse events End of follow-up 6 Important	Relative risk 2.61 (CI 95% 1.67 – 4.07) Based on data from 105 patients in 1 studies. ⁵	300 per 1000 Difference:	783 per 1000 483 more per 1000 (CI 95% 201 more – 921 more)	Very low Due to very serious imprecision, Due to serious risk of bias ⁶	1 study found a statistically significant increase in adverse events with colchicine compared with standard care.
Clinical progression (scale) Increase of 2 grades on 7-grade scale; 21 days after commencing treatment 6 Important	Relative risk 0.13 (CI 95% 0.02 – 1.02) Based on data from 105 patients in 1 studies. ⁷ (Randomized controlled)	140 per 1000 Difference:	18 per 1000 122 fewer per 1000 (CI 95% 137 fewer – 3 more)	Very low Due to serious risk of bias, Due to very serious imprecision ⁸	1 study found no statistically significant difference in clinical progression with colchicine compared with standard care.
ICU admission Within 21 days of starting treatment 6 Important	Relative risk 0.33 (CI 95% 0.04 – 3.06) Based on data from 72 patients in 1 studies. ⁹ (Randomized controlled)	83 per 1000 Difference:	27 per 1000 56 fewer per 1000 (CI 95% 80 fewer – 171 more)	Very low Due to serious risk of bias, Due to very serious imprecision ¹⁰	1 study found no statistically significant difference in ICU admission with colchicine compared with standard care.
Discharge from hospital 10 days after starting treatment 6 Important	Relative risk 1.5 (CI 95% 1.14 – 1.98) Based on data from 72 patients in 1 studies. ¹¹ (Randomized controlled)	611 per 1000 Difference:	917 per 1000 306 more per 1000 (CI 95% 86 more – 599 more)	Very low Due to serious risk of bias, Due to very serious imprecision ¹²	1 study found a statistically significant increase in discharge from hospital at day 10 with colchicine compared with standard care.
Duration of hospital stay Days 6 Important	Lower better Based on data from: 100 patients in 1 studies. (Randomized controlled)	8.12 (Mean) Difference:	6.28 (Mean) MD 1.84 lower CI 95%	Very low Due to very serious risk of bias, Due to serious imprecision ¹³	1 study found shorter duration of hospital stay with colchicine compared with placebo.

1. Systematic review [44] with included studies: Lopes 2021, Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.

2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Only data from one study, Wide confidence intervals, Low number of patients, due to low numbers of events.
3. Systematic review [44] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Only data from one study, Low number of patients, Wide confidence intervals, due to few events.
5. Systematic review [44] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.
7. Systematic review [44] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to [reason], due to [reason].
9. Systematic review [44] with included studies: Lopes 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, Low number of patients, due to few events, due to [reason], due to [reason].
11. Systematic review [44] with included studies: Lopes 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, Low number of patients.
13. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: serious.** Wide confidence intervals, Only data from one study.

Only in research settings

Only use colchicine to treat COVID-19 in community settings as part of a clinical trial.

Evidence To Decision

Benefits and harms

Important harms

The panel considered the results from a study of colchicine for COVID-19 in people in the community. It was not possible to determine whether it was beneficial or harmful because too few of the primary outcomes were reached (that is, few people died, needed mechanical ventilation or were admitted to hospital). Although the overall estimates of effect suggested possible benefit, the confidence intervals included the possibility of both benefit and harm. The panel were aware that the UK-based [PRINCIPLE randomised controlled trial](#) is currently recruiting people with COVID-19 in the community and

colchicine is one of the treatment options.

Adverse events such as diarrhoea were higher with colchicine than with placebo in the identified evidence. The panel noted that colchicine commonly causes diarrhoea, which can lead to potassium deficiency (hypokalaemia). They advised that, because of the adverse effects, colchicine tends to be used in general practice for the treatment of gout for 3 to 4 days.

Certainty of the Evidence

Low

The overall certainty of the evidence for colchicine for COVID-19 in people in community settings is low because of few outcome events and wide confidence intervals.

Preference and values

We expect few to want the intervention

The panel were not aware of any systematically collected data on peoples' preferences and values.

The panel thought that people would not want to take a treatment with no known benefits but well-established side effects such as diarrhoea. However, people might be willing to take colchicine in the context of research.

Resources

No important issues with the recommended alternative

Cost effectiveness was not assessed as part of the evidence review.

Colchicine costs from £1.73 for 28 tablets (BNF, April 2021). The panel therefore expected a negligible effect on resources.

Equity

No important issues with the recommended alternative

Colchicine should not be used in pregnancy and no studies in children were identified. However, because the overall recommendation to use colchicine only in research applies to all ages and subgroups, it is not expected to cause inequity among any subgroups.

Acceptability

Intervention is likely poorly accepted

The panel were not aware of any systematically collected evidence about acceptability.

Colchicine is not licensed in the UK for treating COVID-19. The panel noted that its side effects are unlikely to be acceptable to patients or prescribers, especially diarrhoea and hypokalaemia. The panel noted that diarrhoea is particularly concerning in older people because frequent toilet visits and dehydration could be a risk factor for falls.

Feasibility

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about feasibility.

Colchicine is not used for treating COVID-19 in the UK, so the recommendation supports current practice as well as supporting further research in this area.

Rationale

The evidence on the benefits and harms of colchicine to treat COVID-19 in adults in community settings was inconclusive. This was because too few of the primary outcomes were reached (that is, the number of people who died, needed mechanical ventilation or were admitted to hospital). Although the overall estimates of effect suggested possible benefit, the confidence intervals included the possibility of both benefit and harm. The UK-based [PRINCIPLE randomised controlled trial](#) is currently

recruiting adults with COVID-19 having treatment in community settings, with colchicine as one of the possible treatments. The panel agreed that colchicine should only be used to treat COVID-19 in community settings as part of a clinical trial to support recruitment into this trial.

There is no evidence for colchicine to treat COVID-19 in children and young people in community settings, and no relevant ongoing trial. The recommendation applies to all age groups so that children and young people are not excluded from any future trial.

Clinical Question/ PICO

Population:	People with COVID-19 in the community
Intervention:	Colchicine
Comparator:	Placebo

Summary

There remains uncertainty whether colchicine is more effective than placebo and acceptably safe in treating patients with COVID-19 in the community setting.

What is the evidence informing this conclusion?

Evidence comes from Tardiff et al. (2021) (COLCORONA trial) [49] that compared colchicine with placebo in 4488 adults with confirmed COVID-19 in the community who had known risk factors for poor outcomes, such as obesity, diabetes or uncontrolled hypertension.

Publication status

The study was only available as a preprint and has therefore not been peer reviewed.

Study characteristics

The mean age of participants was 55 years and the proportion of women was 54%. The report did not clearly define the severity of COVID-19.

The dosage of colchicine was 0.5 mg twice daily for the first 3 days then once daily for 27 days. No concomitant drug treatments were reported.

Follow-up was 30 days after starting treatment.

Pregnant and breastfeeding women were excluded from all studies. No children were included.

What are the main results?

For the critical outcomes of mortality and need for mechanical ventilation, there was no statistically significant effect 30 days after starting colchicine treatment compared with placebo. There were too few events to determine whether colchicine makes a difference and the confidence interval includes the possibility of benefit or harm.

There was no statistically significant difference in the important outcome of admission to hospital at 30 days with colchicine compared with placebo.

The important outcomes of adverse events and serious adverse events at the end of follow-up showed conflicting results. Statistically significantly higher overall levels of adverse events were seen at the end of follow-up with colchicine compared with placebo. However, for serious adverse events, borderline statistically significantly lower rates were reported in the colchicine group compared with placebo.

In terms of specific adverse events reported in the study:

- serious pneumonia was statistically significantly increased in the placebo group
- serious gastrointestinal adverse events showed no statistically significant difference between groups
- pulmonary embolism, diarrhoea and rash were statistically significantly more frequent in the colchicine group
- nausea and gastrointestinal haemorrhage showed no statistically significant difference between groups.

The duration of follow-up for adverse events was 30 days after starting treatment.

Our confidence in the results

The certainty of evidence was rated as low for the critical outcomes of all-cause mortality and mechanical ventilation because of very serious imprecision in that only one study was identified, there were few events and confidence intervals were wide.

Adverse events and serious adverse events were rated as low certainty because of serious imprecision due to wide confidence intervals and serious inconsistency due to opposite direction of effect of these outcomes.

Admission to hospital was rated as low certainty because of serious imprecision – only one study was identified and confidence intervals were wide.

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Colchicine	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality 30 days 9 Critical	Relative risk 0.56 (CI 95% 0.19 – 1.67) Based on data from 4,488 patients in 1 studies. ¹ (Randomized controlled)	4 per 1000 Difference:	2 per 1000 2 fewer per 1000 (CI 95% 3 fewer – 3 more)	Low Due to very serious imprecision ²	1 study found no statistically significant difference in all-cause mortality at 30 days with colchicine compared with placebo.
Mechanical ventilation 30 days 9 Critical	Relative risk 0.53 (CI 95% 0.26 – 1.09) Based on data from 4,488 patients in 1 studies. ³ (Randomized controlled)	9 per 1000 Difference:	5 per 1000 4 fewer per 1000 (CI 95% 7 fewer – 1 more)	Low Due to very serious imprecision ⁴	1 study found no statistically significant difference in mechanical ventilation at 30 days with colchicine compared with placebo.
Adverse events 30 days 6 Important	Relative risk 1.56 (CI 95% 1.38 – 1.76) Based on data from 4,412 patients in 1 studies. ⁵ (Randomized controlled)	155 per 1000 Difference:	242 per 1000 87 more per 1000 (CI 95% 59 more – 118 more)	Low Due to serious inconsistency, Due to serious imprecision ⁶	1 study found a statistically significant increase in adverse events at 30 days with colchicine compared with placebo.
Serious adverse events 30 days 6 Important	Relative risk 0.78 (CI 95% 0.61 – 1) Based on data from 4,412 patients in 1 studies. ⁷ (Randomized controlled)	63 per 1000 Difference:	49 per 1000 14 fewer per 1000 (CI 95% 25 fewer – 0 fewer)	Low Due to serious inconsistency, Due to serious imprecision ⁸	1 study found a statistically significant reduction in serious adverse events at 30 days with colchicine compared with placebo.
Admission to hospital 30 days 6 Important	Relative risk 0.8 (CI 95% 0.62 – 1.03) Based on data from 4,488 patients in 1 studies. (Randomized controlled)	57 per 1000 Difference:	46 per 1000 11 fewer per 1000 (CI 95% 22 fewer – 2 more)	Low Due to very serious imprecision ⁹	1 study found no statistically significant difference in admission to hospital at 30 days with colchicine compared with placebo.

1. Systematic review [45] with included studies: Tardif 2021. **Baseline/comparator:** Control arm of reference used for intervention.

2. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, due to few events.

3. Systematic review [45] with included studies: Tardif 2021. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, due to few events.

5. Systematic review [45] with included studies: Tardif 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: serious.** due to opposite direction of effect to serious adverse effects. **Imprecision: serious.** Only data from one study.
7. Systematic review [45] with included studies: Tardif 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: serious.** due to opposite direction of effect to overall adverse events. **Imprecision: serious.** Only data from one study.
9. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.

References

45. Meta-analysis of colchicine for COVID-19 in the community- April 2021.

7.12 Doxycycline

Not recommended

Do not use doxycycline to treat COVID-19 in the community.

Evidence To Decision

Benefits and harms

Important harms

The panel discussed evidence from a trial comparing doxycycline plus standard care with standard care alone to treat COVID-19 in the community in people 65 years and over or people 50 and over if they have comorbidities. They agreed that the evidence suggests that, in these groups, doxycycline plus standard care does not reduce the risk of hospitalisation and death, admission into intensive care, the need for mechanical ventilation or oxygen, or significant adverse events. They also agreed that the evidence suggests doxycycline does not improve symptoms or recovery. The panel noted the lack of statistically significant benefits with doxycycline in both the main analysis population and the analysis in people with laboratory-confirmed positive COVID-19. The panel were aware that randomisation to doxycycline in the trial was stopped because of futility in December 2020. No evidence was identified for other groups or settings.

The panel noted that doxycycline may cause side effects such as gastrointestinal disturbances and photosensitivity. They were also concerned that using doxycycline to treat COVID-19 in the community may increase risk of antimicrobial resistance, which could have important antibiotic stewardship implications.

Certainty of the Evidence

Moderate

The certainty of evidence was rated as moderate because of serious imprecision (apart from 1 outcome that was rated as high). The panel were aware of imprecision issues, including there being only 1 study, the confidence intervals crossing the line of no effect and few events for some outcomes.

The panel were unclear on which symptoms were included in the measures of symptom alleviation and recovery.

The panel also discussed the relatively low proportion of people in the trial with laboratory-confirmed COVID-19. They thought this reflected the pragmatic treatment of COVID-19 in the community in the early stages of the pandemic, which was based on the presence of symptoms and limited testing capacity. However, they noted that testing is now more widely available in the community.

Because there are potential harms from doxycycline use (side effects and risk of antimicrobial resistance), the panel made a strong recommendation against use in the community.

Preference and values

We expect few to want the intervention

The panel were not aware of any systematically collected data on peoples' preferences and values. They noted the importance to people with COVID-19 in the community of avoiding hospital admission. However, the included trial only reported a composite outcome of hospitalisation and death, and reported hospital assessment without admission but not hospitalisation. Avoiding admission into intensive care was also considered an important outcome by the panel. They inferred that most people would not choose doxycycline because of the lack of meaningful benefit in treating COVID-19, the potential for side effects and the risk of antimicrobial resistance.

Resources

Important issues, or potential issues not investigated

Cost effectiveness was not assessed as part of the evidence review.

Equity

No important issues with the recommended alternative

No evidence was found in people under 65 years, people under 50 years with comorbidities or pregnant women. However, because the overall recommendation is not to offer doxycycline to anyone in the community, it is not expected to cause inequity among any groups.

Acceptability

Intervention is likely poorly accepted

The panel were not aware of any systematically collected evidence about acceptability. However, the evidence does not suggest benefits with doxycycline and there are potential harms (from side effects and a risk of promoting antimicrobial resistance). So, its use in the community is not likely to be acceptable unless there are other licensed indications for which its use remains appropriate.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility.

Rationale

There is evidence from 1 trial in the community of doxycycline for COVID-19 in people 65 years and over and in people 50 years and over with comorbidities. The results suggest that, compared with standard care alone, doxycycline plus standard care does not reduce the risk of hospitalisation and death, admission to intensive care, the need for mechanical ventilation or oxygen, or significant adverse events in these groups. The results also suggest that it does not improve symptoms or recovery.

There is no evidence for doxycycline use in the community for COVID-19 in people under 65 years or people under 50 years with comorbidities. But, it is unlikely that the results in these groups will differ, so the panel agreed that the recommendation applies to all age groups in the community. They also noted the risks of side effects and antimicrobial resistance with doxycycline. There was no evidence found for doxycycline use in hospital settings.

Clinical Question/ PICO

Population: People with COVID-19 (Community)
Intervention: Doxycycline plus standard care

Comparator: Standard care

Summary

The evidence suggests that doxycycline plus standard care does not give statistically significant improvements in hospitalisation/death, mechanical ventilation, oxygen administration, ICU admission, measures of symptom alleviation and recovery, or significant adverse events in people with COVID-19 in the community.

What is the evidence informing this conclusion?

These findings are based on 1 RCT (PRINCIPLE) (Butler 2021). This UK study recruited participants from the community with ongoing symptoms (starting within the last 14 days) from PCR-confirmed or suspected COVID-19. Participants were aged 65 years and above or aged 50 years and above with comorbidities.

The RCT compared doxycycline plus standard care (N=780) with standard care (N=948) in adults with COVID-19. In December 2020 randomisation to doxycycline was stopped as pre-specified futility criteria were met.

Publication status

All studies have been peer-reviewed.

Study characteristics

Participants were recruited from the community (from general practices, online, or by telephone). Eligible participants had ongoing symptoms from PCR-confirmed or suspected COVID-19 (that must have started within the last 14 days) (in accordance with the United Kingdom [UK] National Health Service [NHS] definition of high temperature and/or new, continuous cough and/or change in sense of smell/taste). Eligible participants were aged 65 years and older, or 50 years and older if they had comorbidities (weakened immune system; heart disease; hypertension; asthma or lung disease; diabetes; hepatic impairment; stroke or neurological problem; and self-reported obesity or body mass index ≥ 35 kg/m².) People who were already taking acute antibiotics were excluded.

The intervention was doxycycline 200mg on day one, followed by 100mg daily for six days. Standard care for suspected uncomplicated COVID-19 in the community in the UK NHS is largely supportive (antibiotics only being recommended for suspected COVID-19 pneumonia if bacterial aetiology is suspected or the patient is at high risk, in which instance guidelines recommend doxycycline).

The proportion of people with a positive swab result varied from 35.1% (standard care group) to 55.4% (doxycycline group). Participants had a mean (standard deviation [SD]) age of 61.1 (7.9) years; over half (55.7%) were female and the majority (87.2%) had comorbidities. The median (interquartile range [IQR]) duration of illness prior to randomisation was 6 (4–9) days.

What are the main results?

Hospitalisation/death within 28 days (critical outcome)

One RCT (Butler 2021) found no statistically significant difference in hospitalisation/death within 28 days with doxycycline plus standard care compared with standard care (7 more per 1000 patients; RR 1.13 [95% CI 0.73 – 1.74]) in people with COVID-19 in the community

Mechanical ventilation (critical outcome)

One RCT (Butler 2021) reported no statistically significant difference in mechanical ventilation within 28 days with doxycycline plus standard care compared with standard care (4 fewer per 1000 patients; RR 0.49 [95% CI 0.12 – 2.05]) in people with COVID-19 in the community.

Significant adverse events (critical outcome)

One RCT (Butler 2021) showed no statistically significant difference in significant adverse events with doxycycline plus standard care compared with standard care (5 fewer per 1000; RR 0.11 [95% CI 0.01 – 1.99]) in people with COVID-19 in the community.

Oxygen administration (important outcome)

One RCT (Butler 2021) reported no statistically significant difference in oxygen administration within 28 days with doxycycline plus standard care compared with standard care (1 fewer per 1000 patients; RR 0.98 [95% CI 0.55 – 1.76]) in people with COVID-19 in the community

ICU admission (important outcome)

One RCT (Butler 2021) found no statistically significant difference in ICU admission within 28 days with doxycycline plus standard care compared with standard care (5 fewer per 1000; RR 0.55 [95% CI 0.16 – 1.93]) in people with

COVID-19 in the community.

Alleviation of all symptoms within 28 days (important outcome)

One RCT (Butler 2021) found a non statistically significant improvement in alleviation of symptoms within 28 days with doxycycline plus standard care compared with standard care (28 fewer per 1000; RR 0.97 [95% CI 0.94 – 1.00]) in people with COVID-19 in the community.

Initial reduction of severity of symptoms within 28 days (important outcome)

One RCT (Butler 2021) found no statistically significant difference of initial reduction of severity of symptoms within 28 days with doxycycline plus standard care compared with standard care (11 more per 1000; RR 1.01 [95% CI 0.98 – 1.05]) in people with COVID-19 in the community.

Sustained alleviation of all symptoms within 28 days (important outcome)

One RCT (Butler 2021) found no statistically significant difference in alleviation of all symptoms within 28 days with doxycycline plus standard care compared with standard care (5 more per 1000; RR 1.01 [95% CI 0.96 – 1.06]) in people with COVID-19 in the community.

Sustained recovery (important outcome)

One RCT (Butler 2021) found no statistically significant difference in sustained recovery within 28 days with doxycycline plus standard care compared with standard care (29 more per 1000; RR 1.05 [95% CI 0.97– 1.13]) in people with COVID-19 in the community.

Time to initial reduction of severity of symptoms (important outcome)

One RCT (Butler 2021) reported no statistically significant difference in time to initial reduction of severity of symptoms with doxycycline plus standard care (HR 0.99 [95% CI 0.88 – 1.11]) compared with standard care in people with COVID-19 in the community.

Time to alleviation of all symptoms (important outcome)

There was no statistically significant difference in time to alleviation of all symptoms with doxycycline plus standard care compared with standard care (HR 0.96 [95% CI 0.86 – 1.09]) in 1 RCT (Butler 2021) in people with COVID-19 in the community.

Time to sustained alleviation of all symptoms (important outcome)

There was no statistically significant difference in 1 RCT (Butler 2021) for time to initial reduction of severity of symptoms with doxycycline plus standard care compared with standard care (HR 1.03 95% CI 0.90 – 1.17]) in people with COVID-19 in the community.

Time to first reported recovery (important outcome)

One RCT (Butler 2021) showed no statistically significant difference in time to first reported recovery with doxycycline plus standard care compared with standard care (HR 1.04 [95% CI 0.93 – 1.17]) in people with COVID-19 in the community.

Time to sustained recovery (important outcome)

One RCT (Butler 2021) found no statistically significant difference in time to sustained recovery with doxycycline plus standard care compared with standard care (HR 1.00 95 CI 0.88 – 1.14]) in people with COVID-19 in the community.

Our confidence in the results

The certainty of evidence for the critical outcomes of hospitalisation/death, mechanical ventilation and significant adverse events was rated as moderate (due to serious imprecision).

The certainty of evidence for the important outcome of alleviation of all symptoms at 28 days was considered to be high. However, the certainty of evidence for all remaining important outcomes was rated as moderate due to serious imprecision.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Doxycycline plus standard care	Certainty of the Evidence (Quality of evidence)	Plain language summary
Hospitalisation/ death Within 28 days 9 Critical	Relative risk 1.13 (CI 95% 0.73 – 1.74) Based on data from 1,728 patients in 1 studies. ¹ (Randomized controlled)	45 per 1000 Difference:	52 per 1000 7 more per 1000 (CI 95% 11 fewer – 34 more)	Moderate Due to serious imprecision ²	One study found no statistically significant difference in hospitalisation/death within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Mechanical ventilation Within 28 days 9 Critical	Relative risk 0.49 (CI 95% 0.12 – 2.05) Based on data from 1,378 patients in 1 studies. ³ (Randomized controlled)	8 per 1000 Difference:	4 per 1000 4 fewer per 1000 (CI 95% 7 fewer – 8 more)	Moderate Due to serious imprecision ⁴	One study found no statistically significant difference in mechanical ventilation within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Significant adverse events 9 Critical	Relative risk 0.11 (CI 95% 0.01 – 1.99) Based on data from 1,728 patients in 1 studies. ⁵ (Randomized controlled)	5 per 1000 Difference:	0 per 1000 5 fewer per 1000 (CI 95% 5 fewer – 5 more)	Moderate Due to serious imprecision ⁶	One study found no statistically significant difference in significant adverse events with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Oxygen administration Within 28 days 6 Important	Relative risk 0.98 (CI 95% 0.55 – 1.76) Based on data from 1,378 patients in 1 studies. ⁷ (Randomized controlled)	32 per 1000 Difference:	31 per 1000 1 fewer per 1000 (CI 95% 14 fewer – 24 more)	Moderate Due to serious imprecision ⁸	One study found no statistically significant difference in oxygen administration within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
ICU admission Within 28 days 6 Important	Relative risk 0.55 (CI 95% 0.16 – 1.93) Based on data from 1,375 patients in 1 studies. ⁹ (Randomized controlled)	10 per 1000 Difference:	5 per 1000 5 fewer per 1000 (CI 95% 8 fewer – 9 more)	Moderate Due to serious imprecision ¹⁰	One study found no statistically significant difference in ICU admission within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Alleviation of all symptoms Within 28 days	Relative risk 0.97 (CI 95% 0.94 – 1) Based on data from 1,222 patients in 1 studies. ¹¹ (Randomized	947 per 1000 Difference:	921 per 1000 28 fewer per 1000	High ¹²	One study found a non-statistically significant improvement in alleviation of all symptoms within 28

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Doxycycline plus standard care	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important	controlled)		(CI 95% 57 fewer — 75 more)		days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Initial reduction of severity of symptoms Within 28 days	Relative risk 1.01 (CI 95% 0.98 — 1.05) Based on data from 1,424 patients in 1 studies. ¹³ (Randomized controlled)	888 per 1000 Difference:	899 per 1000 11 more per 1000 (CI 95% 18 fewer — 44 more)	Moderate Due to serious imprecision ¹⁴	One study found no statistically significant difference in initial reduction of severity of symptoms within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
6 Important					
Sustained alleviation of all symptoms Within 28 days	Relative risk 1.01 (CI 95% 0.96 — 1.06) Based on data from 1,163 patients in 1 studies. ¹⁵ (Randomized controlled)	831 per 1000 Difference:	836 per 1000 5 more per 1000 (CI 95% 33 fewer — 50 more)	Moderate Due to serious imprecision ¹⁶	One study found no statistically significant difference in sustained alleviation of all symptoms within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community
6 Important					
Sustained recovery Within 28 days	Relative risk 1.05 (CI 95% 0.97 — 1.13) Based on data from 1,424 patients in 1 studies. ¹⁷ (Randomized controlled)	615 per 1000 Difference:	644 per 1000 29 more per 1000 (CI 95% 18 fewer — 80 more)	Moderate Due to serious imprecision ¹⁸	One study found no statistically significant difference in sustained recovery within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community
6 Important					
Time to initial reduction of severity of symptoms	Hazard Ratio 0.99 (CI 95% 0.88 — 1.11) Based on data from 1,424 patients in 1 studies. (Randomized controlled)			Moderate Due to serious imprecision ¹⁹	One study found no statistically significant difference in time to initial reduction of severity of symptoms with doxycycline plus standard care compared with standard care in people with COVID-19 in the community
6 Important					
Time to alleviation of all symptoms	Hazard Ratio 0.96 (CI 95% 0.86 — 1.09) Based on data from 1,222 patients in 1 studies. (Randomized controlled)			Moderate Due to serious imprecision ²⁰	One study found no statistically significant difference in time to alleviation of all symptoms with doxycycline plus standard care compared
6 Important					

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Doxycycline plus standard care	Certainty of the Evidence (Quality of evidence)	Plain language summary
					with standard care in people with COVID-19 in the community
Time to sustained alleviation of all symptoms 6 Important	Hazard Ratio 1.03 (CI 95% 0.9 – 1.17) Based on data from 1,163 patients in 1 studies. (Randomized controlled)			Moderate Due to serious imprecision ²¹	One study found no statistically significant difference in time to sustained alleviation of all symptoms with doxycycline plus standard care compared with standard care in people with COVID-19 in the community
Time to first reported recovery 6 Important	Hazard Ratio 1.04 (CI 95% 0.93 – 1.17) Based on data from 1,728 patients in 1 studies. (Randomized controlled)			Moderate Due to serious imprecision ²²	One study found no statistically significant difference in time to first reported recovery with doxycycline plus standard care compared with standard care in people with COVID-19 in the community
Time to sustained recovery 6 Important	Hazard Ratio 1 (CI 95% 0.88 – 1.14) Based on data from 1,424 patients in 1 studies. (Randomized controlled)			Moderate Due to serious imprecision ²³	One study found no statistically significant difference in time to sustained recovery with doxycycline plus standard care compared with standard care in people with COVID-19 in the community

1. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
3. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to confidence intervals crossing line of no effect.
5. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study.
7. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
9. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to confidence intervals crossing line of no effect.
11. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for

intervention.

12. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Only data from one study.

13. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.

14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.

15. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.

16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.

17. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.

19. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.

20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.

21. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.

22. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.

23. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.

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77. Doxycycline for suspected or confirmed COVID-19.

7.13 Ivermectin

Only in research settings

New

Do not use ivermectin to treat COVID-19 except as part of a clinical trial.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Hospital settings

The panel stated that mortality is an important outcome. They noted that the evidence does not show a statistically significant difference in mortality for people in hospital with COVID-19 having ivermectin compared with people having standard care. They also considered that the certainty of evidence for this outcome is very low.

Although the evidence suggests a statistically significant reduction in duration of hospitalisation for people with COVID-19 who have ivermectin, the panel had concerns with the results. They noted that the certainty of evidence is very low for that

outcome. They also agreed that there are issues with the applicability of the evidence in the hospital setting. This was because most people in the studies had less severe COVID-19 than people who would be hospitalised in the UK.

The panel agreed that the evidence shows no difference between ivermectin and control for the other critical outcomes of admission to intensive care, need for invasive mechanical ventilation, discharge from hospital and adverse events.

The panel discussed the evidence suggesting statistically significant benefits with ivermectin for COVID-19 in people in hospital for viral clearance (at 7 to 12 days), duration to viral clearance and duration of symptoms. However, they agreed that the evidence supporting these benefits is of low to very low certainty. The panel suggested that the value of any benefits in viral clearance might lead to reduced infectivity or viral shedding but considered that this is uncertain. They also agreed that the evidence shows no statistically significant benefits for the other important outcomes of number of people needing oxygen, clinical improvement, clinical worsening, time to recovery and viral clearance (at 1 to 7 days).

Community settings

The panel discussed the evidence on ivermectin use for people with COVID-19 in the community. They agreed the evidence shows no statistically significant differences for ivermectin in: mortality; need for invasive mechanical ventilation; adverse events; need for hospitalisation; number of people needing oxygen; clinical progression; clinical recovery; presence of symptoms at day 7; viral clearance (at 7 to 12 days); virological clearance (within 14 days); or recovery. The panel noted that the certainty of evidence is low to very low for all outcomes.

The panel also noted that evidence suggests a statistically significant increase in stopping treatment because of adverse events with ivermectin but agreed that this evidence is of very low certainty.

Other panel considerations

The panel discussed the potential for the occurrence of rare serious adverse events with ivermectin. They considered that the available studies were too small to identify such events.

The panel noted that no studies were from the UK. They commented that some of the treatments (such as hydroxychloroquine, doxycycline, azithromycin and lopinavir–ritonavir) used in the control groups are not used in the UK for COVID-19. Detail on other treatments was lacking in some studies. The panel considered that this limits the applicability of the evidence to UK practice. The panel also discussed that, because dosage varied widely across the included studies, it is uncertain what a safe dose of ivermectin would be.

The panel agreed that the uncertainty around the benefits and safety of ivermectin based on the current evidence means that it cannot be recommended for COVID-19 in people in hospital or community settings. They considered that this was the case for children, young people and adults. The panel were aware of ongoing trials investigating ivermectin, such as the PRINCIPLE trial. They considered that the available evidence for the effectiveness and safety of ivermectin could be improved by evidence from a well-designed randomised controlled trial.

Certainty of the Evidence

Very low

The panel agreed that the certainty of evidence on ivermectin for people with COVID-19 in hospital and in the community is low to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with most studies being at high or unclear risk of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care differing from that in the UK); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). Some studies were only available as preprints so have not been peer reviewed.

Preference and values

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on peoples' preferences and values about ivermectin for COVID-19. They discussed that people with COVID-19 may have different views on ivermectin use because of the quality of current evidence, uncertainty over its safety and the availability of recommended treatments for COVID-19 in the UK.

Resources

Important issues, or potential issues not investigated

The panel raised concerns about ivermectin being used to treat COVID-19 when there is limited evidence of benefit. They highlighted the importance of not diverting resources away from other evidence-based indications for ivermectin.

Cost effectiveness was not assessed as part of the evidence review.

Equity

Important issues, or potential issues not investigated

No evidence was found for ivermectin use in pregnancy. Limited evidence was identified in children or young people. However, because the overall recommendation is not to offer ivermectin, it is not expected to cause inequity among any groups. The panel considered the issue of equity and did not raise any additional concerns. However, the panel flagged the importance of not diverting ivermectin supply away from existing evidence-based indications in non-UK countries.

Acceptability

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about acceptability. Ivermectin is not licensed in the UK for treating COVID-19. The low to very low certainty of current evidence may reduce acceptability.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility. However, the panel noted the current limited availability of ivermectin in the UK.

Rationale

Overall, there is a high degree of uncertainty about whether ivermectin is more effective than control for managing COVID-19 in hospital or community settings. The panel raised concerns about the quality of the studies on ivermectin. They agreed that the certainty of evidence is low to very low for all outcomes. The panel also noted the uncertainty about the overall safety and the possibility of rare serious adverse events with ivermectin. Because of the uncertainty in the current evidence (including small sample sizes and issues with study quality), the panel concluded that ivermectin should only be used to treat COVID-19 in well-conducted clinical trials.

Clinical Question/ PICO

Population: People with COVID-19 (Community)
Intervention: Ivermectin
Comparator: Standard care, standard care plus placebo, or placebo

Summary

There remains a high degree of uncertainty over whether ivermectin is more effective than placebo, placebo plus standard care or standard care for management of COVID-19 in the community.

What is the evidence informing this conclusion?

Evidence comes from 7 randomised control trials (RCTs) that compared ivermectin with placebo, placebo plus standard care or standard care in people with COVID-19 in the community (Biber 2021; Buonfrate 2021; Chaccour 2021; Chachar 2020; Lopez-Medina 2021; Podder 2021; Vallejos 2021).

Publication status

Two studies were preprints (posted on medRxiv on 31 May 2021 (Biber 2021) and posted on Lancet preprints on 6 September 2021 (Buonfrate 2021) and have therefore not been peer reviewed.

Five studies were full publications (Chaccour 2021; Chachar 2020; Lopez-Medina 2021; Podder 2021; Vallejos 2021).

Study characteristics

Sample sizes ranged from 24 (Chaccour 2021) to 501 (Vallejos 2021). The average age of study samples ranged from 26 (Chaccour 2021) to 47 years (Buonfrate 2021). Study samples were mostly male. Standard care within the trials varied.

For COVID-19 disease severity (based on degree of respiratory support): 88% were mild/moderate, 11% asymptomatic and 0.15% severe. The studies defined COVID-19 disease severity using a variety of markers.

Participants were described as outpatients in 2 studies (Buonfrate 2021; Podder 2021), attending COVID-19 clinics and the outpatient department in 1 study (Chachar 2020) and as being non-hospitalised in 2 studies (Biber 2021, Vallejos 2021). In 1 study people were described as attending the emergency room and the trial protocol stated patients isolated at home (Chaccour 2021). One study was a mixed setting of home or hospital, but very few people were hospitalised (Lopez-Medina 2021).

Ivermectin doses varied across the included studies.

For further details see the evidence review.

What are the main results?

Critical outcomes

Discontinuation of treatment due to adverse events was significantly higher with ivermectin compared with control.

The evidence suggests that, compared with control groups in people with COVID-19 in the community, ivermectin does not result in statistically significant differences in any other critical outcomes reviewed.

Important outcomes

No statistically significant differences were seen with ivermectin compared with control in the important outcomes reviewed.

Our confidence in the results

Studies are heterogenous with both clinical and methodological diversity. For some studies insufficient information was available to assess the methods used. Most studies were assessed as being at high or unclear risk of bias. Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care differing from that in the UK); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). Certainty of evidence was low or very low for all outcomes.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality (day 28) 9 Critical	Relative risk 1 (CI 95% 0.27 – 3.67) Based on data from 899 patients in 2 studies. ¹ (Randomized controlled)	9 per 1000 Difference:	9 per 1000 0 fewer per 1000 (CI 95% 7 fewer – 24 more)	Very low Due to serious indirectness, Due to serious imprecision, Due to serious inconsistency, Due to very serious risk of bias ²	2 studies showed no significant difference in mortality for ivermectin compared with control.
Invasive mechanical ventilation 9 Critical	Relative risk 1.34 (CI 95% 0.3 – 5.92) Based on data from 501 patients in 1 studies. ³ (Randomized controlled)	12 per 1000 Difference:	16 per 1000 4 more per 1000 (CI 95% 8 fewer – 59 more)	Low Due to serious imprecision, Due to serious indirectness ⁴	1 study showed no significant difference in invasive mechanical ventilation for ivermectin compared with control.
Hospitalisation (with Buonfrate lower dose) 9 Critical	Relative risk 0.65 (CI 95% 0.35 – 1.19) Based on data from 634 patients in 3 studies. ⁵ (Randomized controlled)	78 per 1000 Difference:	51 per 1000 27 fewer per 1000 (CI 95% 51 fewer – 15 more)	Very low Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision ⁶	3 studies showed no significant difference in hospitalisation for ivermectin compared with control.
Hospitalisation (with Buonfrate higher dose) 9 Critical	Relative risk 0.7 (CI 95% 0.39 – 1.27) Based on data from 635 patients in 3 studies. ⁷ (Randomized controlled)	78 per 1000 Difference:	55 per 1000 23 fewer per 1000 (CI 95% 48 fewer – 21 more)	Very low Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision ⁸	3 studies showed no significant difference in hospitalisation for ivermectin compared with control.
Serious adverse events (end of follow-up) (Buonfrate lower dose) 9 Critical	Relative risk 1.17 (CI 95% 0.23 – 6.08) Based on data from 967 patients in 4 studies. ⁹ (Randomized controlled)	4 per 1000 Difference:	5 per 1000 1 more per 1000 (CI 95% 3 fewer – 20 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to very serious risk of bias ¹⁰	4 studies showed no significant difference in serious adverse events for ivermectin compared with control.
Serious adverse events (end of follow-up) (Buonfrate higher dose) 9 Critical	Relative risk 1.68 (CI 95% 0.36 – 7.97) Based on data from 969 patients in 4 studies. ¹¹ (Randomized controlled)	4 per 1000 Difference:	7 per 1000 3 more per 1000 (CI 95% 3 fewer – 28 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to very serious risk of bias ¹²	4 studies showed no significant difference in serious adverse events for ivermectin compared with control.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
Adverse events (end of follow up) 9 Critical	Relative risk 0.92 (CI 95% 0.82 – 1.03) Based on data from 1,039 patients in 4 studies. ¹³ (Randomized controlled)	427 per 1000 Difference:	393 per 1000 34 fewer per 1000 (CI 95% 77 fewer – 13 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to very serious risk of bias ¹⁴	4 studies showed no significant difference in adverse events for ivermectin compared with control.
Discontinuation due to adverse events 9 Critical	Relative risk 2.97 (CI 95% 1.1 – 8.02) Based on data from 899 patients in 2 studies. ¹⁵ (Randomized controlled)	11 per 1000 Difference:	33 per 1000 22 more per 1000 (CI 95% 1 more – 77 more)	Very low Due to serious indirectness, Due to very serious risk of bias ¹⁶	2 studies showed a significant increase in discontinuation due to adverse events for ivermectin compared with control.
Number of patients requiring oxygen 6 Important	Relative risk 0.3 (CI 95% 0.01 – 7.14) Based on data from 89 patients in 1 studies. ¹⁷ (Randomized controlled)	24 per 1000 Difference:	7 per 1000 17 fewer per 1000 (CI 95% 24 fewer – 147 more)	Very low Due to very serious imprecision, Due to serious indirectness, Due to serious risk of bias ¹⁸	1 study showed a non- significant reduction in the number of people requiring oxygen for ivermectin compared with control.
Clinical progression 6 Important	Relative risk 0.57 (CI 95% 0.17 – 1.9) Based on data from 422 patients in 2 studies. ¹⁹ (Randomized controlled)	33 per 1000 Difference:	19 per 1000 14 fewer per 1000 (CI 95% 27 fewer – 30 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to very serious risk of bias ²⁰	2 studies showed no significant difference in clinical progression for ivermectin compared with control.
Clinical recovery (21 days) 6 Important	Relative risk 1.04 (CI 95% 0.94 – 1.15) Based on data from 398 patients in 1 studies. ²¹ (Randomized controlled)	788 per 1000 Difference:	820 per 1000 32 more per 1000 (CI 95% 47 fewer – 118 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to very serious risk of bias ²²	1 study showed no significant difference in clinical recovery for ivermectin compared with control.
Symptomatic at day 7 6 Important	Relative risk 0.9 (CI 95% 0.44 – 1.83) Based on data from 50 patients in 1 studies. ²³ (Randomized controlled)	400 per 1000 Difference:	360 per 1000 40 fewer per 1000 (CI 95% 224 fewer – 332 more)	Very low Due to very serious imprecision, Due to serious indirectness, Due to very serious risk of bias ²⁴	1 study showed no significant difference in people symptomatic at day 7 for ivermectin compared with control.
Viral clearance (7-12 days) 6 Important	Relative risk 0.99 (CI 95% 0.93 – 1.06) Based on data from 630 patients in 3 studies. ²⁵	859 per 1000	850 per 1000	Very low Due to serious imprecision, Due to serious	3 studies showed no significant difference in viral clearance (7 to 12 days) for ivermectin

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important	(Randomized controlled)	Difference:	9 fewer per 1000 (CI 95% 60 fewer — 52 more)	indirectness, Due to serious inconsistency ²⁶	compared with control.
Virological clearance (within 14 days) (Buonfrate lower dose)	Relative risk 1.19 (CI 95% 0.74 — 1.91) Based on data from 43 patients in 1 studies. ²⁷ (Randomized controlled)	600 per 1000	714 per 1000	Very low Due to very serious imprecision, Due to serious indirectness, Due to serious risk of bias ²⁸	1 study showed no significant difference in virological clearance for ivermectin compared with control.
6 Important		Difference:	114 more per 1000 (CI 95% 156 fewer — 546 more)		
Virological clearance (within 14 days) (Buonfrate higher dose)	Relative risk 0.94 (CI 95% 0.56 — 1.59) Based on data from 45 patients in 1 studies. ²⁹ (Randomized controlled)	600 per 1000	564 per 1000	Very low Due to serious risk of bias, Due to very serious imprecision, Due to serious indirectness ³⁰	1 study showed no significant difference in recovery for ivermectin compared with control.
6 Important		Difference:	36 fewer per 1000 (CI 95% 264 fewer — 354 more)		
Recovery (from date of illness onset)	Based on data from: 62 patients in 1 studies. ³¹ (Randomized controlled)	Difference:	MD 1.41 lower (CI 95% 3.62 lower — 0.8 higher)	Very low Due to very serious imprecision, Due to serious indirectness, Due to very serious risk of bias ³²	1 study showed no significant difference in recovery for ivermectin compared with control.
6 Important		Difference:	MD 1.02 lower (CI 95% 2.76 lower — 0.72 higher)	Very low Due to very serious imprecision, Due to serious indirectness, Due to serious risk of bias, Due to very serious risk of bias ³⁴	1 study showed no significant difference in recovery for ivermectin compared with control.
Recovery (from date of enrolment)	Based on data from: 62 patients in 1 studies. ³³ (Randomized controlled)				
6 Important					

1. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
3. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: no serious.** less than 33.3% weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
5. Systematic review [133] with included studies: Biber 2021, Buonfrate 2021 600 ug, Vallejos 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: no serious.** less than 33.3% weight came from studies at unclear or high risk of bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: serious.** standard care not relevant to UK. **Imprecision: serious.** due to confidence

interval crossing line of no effect. **Publication bias: no serious.**

7. Systematic review [133] with included studies: Biber 2021, Buonfrate 2021 1200 ug, Vallejos 2021. **Baseline/comparator:** Control arm of reference used for intervention.

8. **Risk of Bias: no serious.** less than 33.3% weight came from studies at unclear or high risk of bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: serious.** standard care not relevant to UK. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**

9. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

10. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**

11. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

12. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**

13. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

14. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**

15. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

16. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: no serious.** **Publication bias: no serious.**

17. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

18. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**

19. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

20. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**

21. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

22. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**

23. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

24. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**

25. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

26. **Risk of Bias: no serious.** less than 33.3% weight came from studies at unclear or high risk of bias. **Inconsistency: serious.** due to large I-squared value (>50%). **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**

27. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

28. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**

29. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

30. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**

31. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

32. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**

33. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.

34. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence

interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**

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133. Ivermectin versus standard care for COVID-19.

Clinical Question/ PICO

Population:	People with COVID-19 (Hospitalised)
Intervention:	Ivermectin
Comparator:	Standard care, standard care plus placebo, or placebo

Summary

There remains a high degree of uncertainty over whether ivermectin is more effective than placebo, placebo plus standard care or standard care for management of COVID-19 in hospital.

What is the evidence informing this conclusion?

Evidence comes from 11 randomised control trials (RCTs) that compared ivermectin with placebo, placebo plus standard care or standard care for people hospitalised with COVID-19 (Abd-El Salam 2021; Ahmed 2021; Bukhari 2021; Gonzalez 2021; Kishoria 2020; Krolewiecki 2021; Mohan 2021; Pott-Junior 2021; Ravikirti 2021; Shahbaznejad 2021; Shakhshi Niaee 2021).

Publication status

Two studies were preprints (posted to medRxiv on 5 February 2021 (Bukhari 2021), and on 23 February 2021 (Gonzalez 2021) and have therefore not been peer reviewed.

Nine studies were full publications (Abd-El Salam 2021; Ahmed 2021; Kishoria 2020; Krolewiecki 2021; Mohan 2021; Pott-Junior 2021; Ravikirti 2021; Shahbaznejad 2021; Shakhshi Niaee 2021).

Study characteristics

Sample sizes ranged from 31 (Pott-Junior 2021) to 180 (Shakhsi Niaee 2021). The average age of study samples ranged from 35 (Mohan 2021) to 56 years (Gonzalez 2021) and the proportion of women ranged between 10 and 55%. Standard care within the trials varied.

For COVID-19 disease severity (based on degree of respiratory support) the majority of patients were mild/moderate (61%), with 10% severe and 3% asymptomatic. It was not possible to determine severity in 26% of patients. The studies define severity using a variety of measures.

Ivermectin doses varied across the included studies.

For further details see the evidence review.

What are the main results?

Critical outcomes

The evidence suggests that, compared with control groups in people with COVID-19 in hospital, ivermectin does not result in statistically significant differences in the critical outcomes reviewed.

Important outcomes

The evidence suggests that ivermectin does not result in statistically significant differences in number of patients requiring oxygen, clinical improvement, clinical worsening and viral clearance (1-7 days).

The evidence suggests that, compared with control, ivermectin results in a statistically significant reduction in viral clearance (7-12 days), duration of hospitalisation, duration of symptoms and duration to viral clearance.

Our confidence in the results

Studies are heterogenous with both clinical and methodological diversity. For some studies insufficient information was available to assess the methods used. Most studies were assessed as being at high or unclear risk of bias. Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care differing from that in the UK, specifically, the majority of patients had mild/moderate disease so in UK practice would not be hospitalised); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). Certainty of evidence was low or very low for all outcomes.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality (day 28) 9 Critical	Relative risk 0.41 (CI 95% 0.16 – 1.07) Based on data from 681 patients in 5 studies. ¹ (Randomized controlled)	87 per 1000 Difference:	36 per 1000 51 fewer per 1000 (CI 95% 73 fewer)	Very low Due to very serious risk of bias, Due to serious indirectness, Due to serious	5 studies showed a non- significant reduction in mortality for ivermectin compared with control.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
			– 6 more)	imprecision, Due to serious inconsistency ²	
Admission to ICU 9 Critical	Relative risk 0.7 (CI 95% 0.26 – 1.91) Based on data from 143 patients in 2 studies. ³ (Randomized controlled)	115 per 1000 Difference:	81 per 1000 34 fewer per 1000 (CI 95% 85 fewer – 105 more)	Very low Due to serious indirectness, Due to very serious imprecision, Due to serious risk of bias ⁴	2 studies showed no significant difference in admission to ICU for ivermectin compared with control.
Invasive mechanical ventilation 9 Critical	Relative risk 0.75 (CI 95% 0.29 – 1.95) Based on data from 529 patients in 5 studies. ⁵ (Randomized controlled)	38 per 1000 Difference:	29 per 1000 9 fewer per 1000 (CI 95% 27 fewer – 36 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to serious inconsistency, Due to serious risk of bias ⁶	5 studies showed no significant difference in invasive mechanical ventilation for ivermectin compared with control.
Discharge from hospital (end of follow-up) 9 Critical	Relative risk 1.04 (CI 95% 0.97 – 1.12) Based on data from 342 patients in 4 studies. ⁷ (Randomized controlled)	868 per 1000 Difference:	903 per 1000 35 more per 1000 (CI 95% 26 fewer – 104 more)	Very low Due to serious indirectness, Due to serious imprecision, Due to serious risk of bias ⁸	4 studies showed no significant difference in discharge from hospital for ivermectin compared with control.
Discharge from hospital (by day 10) 9 Critical	Relative risk 1.09 (CI 95% 0.89 – 1.33) Based on data from 112 patients in 1 studies. ⁹ (Randomized controlled)	737 per 1000 Difference:	803 per 1000 66 more per 1000 (CI 95% 81 fewer – 243 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision ¹⁰	1 study showed no significant difference in discharge from hospital for ivermectin compared with control.
Serious adverse events (end of follow-up) 9 Critical	Relative risk 1.55 (CI 95% 0.07 – 35.89) Based on data from 242 patients in 3 studies. ¹¹ (Randomized controlled)	0 per 1000 Difference:	0 per 1000 0 fewer per 1000 (CI 95% 0 fewer – 0 fewer)	Very low Due to serious indirectness, Due to very serious imprecision, Due to serious risk of bias ¹²	There were too few who experienced serious adverse events to determine whether ivermectin made a difference.
Adverse events (end of follow up) 9 Critical	Relative risk 1.27 (CI 95% 0.75 – 2.16) Based on data from 592 patients in 7 studies. ¹³ (Randomized controlled)	51 per 1000 Difference:	65 per 1000 14 more per 1000 (CI 95% 13 fewer – 59 more)	Very low Due to serious indirectness, Due to serious imprecision, Due to serious risk of bias ¹⁴	7 studies showed no significant difference in adverse events for ivermectin compared with control.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
Number of patients requiring oxygen 6 Important	Relative risk 1.08 (CI 95% 0.5 – 2.32) Based on data from 114 patients in 2 studies. ¹⁵ (Randomized controlled)	158 per 1000 Difference:	171 per 1000 13 more per 1000 (CI 95% 79 fewer – 209 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision ¹⁶	2 studies showed no significant difference in the number of patients requiring oxygen for ivermectin compared with control.
Clinical improvement (2 or more decrease WHO) 6 Important	Relative risk 1.07 (CI 95% 0.94 – 1.22) Based on data from 125 patients in 1 studies. ¹⁷ (Randomized controlled)	867 per 1000 Difference:	928 per 1000 61 more per 1000 (CI 95% 52 fewer – 191 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision ¹⁸	1 study showed no significant difference in clinical improvement for ivermectin compared with control.
Clinical worsening 6 Important	Relative risk 0.56 (CI 95% 0.17 – 1.84) Based on data from 125 patients in 1 studies. ¹⁹ (Randomized controlled)	111 per 1000 Difference:	62 per 1000 49 fewer per 1000 (CI 95% 92 fewer – 93 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision ²⁰	1 study showed no significant difference in clinical worsening for ivermectin compared with control.
Viral clearance (1-7 days) 6 Important	Relative risk 1.03 (CI 95% 0.55 – 1.91) Based on data from 63 patients in 2 studies. ²¹ (Randomized controlled)	471 per 1000 Difference:	485 per 1000 14 more per 1000 (CI 95% 212 fewer – 429 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision ²²	2 studies showed no significant difference in viral clearance (1 to 7 days) for ivermectin compared with control.
Viral clearance (7-12 days) 6 Important	Relative risk 1.68 (CI 95% 1.26 – 2.25) Based on data from 203 patients in 2 studies. ²³ (Randomized controlled)	378 per 1000 Difference:	635 per 1000 257 more per 1000 (CI 95% 98 more – 473 more)	Very low Due to very serious risk of bias, Due to serious indirectness, Due to serious inconsistency ²⁴	2 studies showed a statistically significant improvement in viral clearance (7 to 12 days) for ivermectin compared with control.
Duration of hospitalisation (days) 9 Critical	Based on data from: 278 patients in 3 studies. ²⁵ (Randomized controlled)	Difference:	MD 1.43 lower (CI 95% 2.41 lower – 0.44 lower)	Very low Due to serious indirectness, Due to very serious risk of bias ²⁶	3 studies showed a statistically significant reduction in duration of hospitalisation for ivermectin compared with control.
Duration of hospitalisation (days)	Lower better Based on data from: 73 patients in 1 studies. (Randomized controlled)	5 (Median) Difference:	6 (Median) 1 higher	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious	It is uncertain whether treatment with ivermectin has an effect on the median duration of hospitalisation compared with control.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
9 Critical				imprecision. ²⁷	
Duration of symptoms 6 Important	Based on data from: 69 patients in 1 studies. ²⁸ (Randomized controlled)	Difference:	MD 1 lower (CI 95% 1.14 lower – 0.86 lower)	Low Due to serious risk of bias, Due to serious indirectness ²⁹	1 study showed a statistically significant reduction in duration of symptoms for ivermectin compared with control.
Time to recovery (resolution of symptoms) 6 Important	Based on data from: 125 patients in 1 studies. ³⁰ (Randomized controlled)	Difference:	MD 0.07 lower (CI 95% 1.09 lower – 0.95 higher)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision ³¹	1 study showed no significant difference in time to recovery for ivermectin compared with control.
Duration to viral clearance 6 Important	Based on data from: 45 patients in 1 studies. ³² (Randomized controlled)	Difference:	MD 3 lower (CI 95% 5.43 lower – 0.57 lower)	Low Due to serious risk of bias, Due to serious indirectness ³³	1 study showed a statistically significant reduction in duration to viral clearance for ivermectin compared with control.

1. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
3. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
5. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
7. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
9. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
11. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
13. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval

crossing line of no effect. **Publication bias: no serious.**

15. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
16. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
17. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
19. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
21. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
23. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
24. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: serious.** due to large I-squared value (>50%). **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: no serious.** **Publication bias: no serious.**
25. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
26. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: no serious.** **Publication bias: no serious.**
27. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to uncertainty in estimate. **Publication bias: no serious.**
28. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
29. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: no serious.** **Publication bias: no serious.**
30. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
31. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
32. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
33. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious.** **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: no serious.** **Publication bias: no serious.**

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133. Ivermectin versus standard care for COVID-19.

7.14 Ongoing review of therapeutics for COVID-19

Info Box

We are currently reviewing new and existing therapeutics for treating COVID-19 as part of a living guidelines approach. New and updated recommendations will be published for this guideline as they become available (see [Update information | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE](#)).

8. Preventing and managing acute complications

8.1 Acute kidney injury (AKI)

Info Box

In people with COVID-19, AKI:

- may be common, but prevalence is uncertain and depends on clinical setting (the [Intensive Care National Audit and Research Centre's report on COVID-19 in critical care](#) provides information on people in critical care who need renal replacement therapy for AKI)
- is associated with an increased risk of dying
- can develop at any time (before, during or after hospital admission)
- may be caused by volume depletion (hypovolaemia), haemodynamic changes, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology or rhabdomyolysis
- may be associated with haematuria, proteinuria and abnormal serum electrolyte levels (both increased and decreased serum sodium and potassium).

Info Box

In people with COVID-19:

- maintaining optimal fluid status (euvolaemia) is difficult but critical to reducing the incidence of AKI
- treatments for COVID-19 may increase the risk of AKI
- treatments for pre-existing conditions may increase the risk of AKI
- fever and increased respiratory rate increase insensible fluid loss.

8.1.1 Assessing and managing acute kidney injury (AKI)

Info Box

The potassium binders patiromer and sodium zirconium cyclosilicate can be used as options alongside standard care for the emergency management of acute life-threatening hyperkalaemia (see [NICE's technology appraisal guidance on patiromer](#) and [sodium zirconium cyclosilicate](#) for treating hyperkalaemia).

Info Box

For information on assessing and managing AKI, see the [NICE guideline on acute kidney injury: prevention, detection and management](#).

For information on using intravenous fluids, see the [NICE guideline on intravenous fluid therapy in adults in hospital](#) and the [NICE guideline on intravenous fluid therapy in children and young people in hospital](#).

For information on managing renal replacement therapy for adults who are critically unwell with COVID-19, see the [Renal Association's guidelines on renal replacement therapy for critically unwell adults](#).

8.1.2 Follow up

Consensus recommendation

Monitor people with chronic kidney disease for at least 2 years after AKI, in line with the [NICE guideline on chronic kidney disease: assessment and management](#).

See guidance on care after hospital discharge in the [Royal College of General Practitioners AKI toolkit](#).

8.2 Acute myocardial injury

8.2.1 Diagnosing acute myocardial injury

Consensus recommendation

For people in hospital with COVID-19 with signs or symptoms that suggest acute myocardial injury, measure high sensitivity troponin I (hs-cTnI) or T (hs-cTnT) and N-terminal pro B-type natriuretic peptide, and do an ECG.

Use the following test results to help inform a diagnosis:

- evolving ECG changes suggesting myocardial ischaemia
- an NT-proBNP level above 400 ng/litre
- high levels of hs-cTnI or hs-cTnT, particularly levels increasing over time.

Info Box

Elevated troponin levels may reflect cardiac inflammatory response to severe COVID-19 rather than acute coronary syndrome.

8.2.2 Managing myocardial injury

Consensus recommendation

For all people with COVID-19 and suspected or confirmed acute myocardial injury:

- monitor in a setting where cardiac or respiratory deterioration can be rapidly identified
- do continuous ECG monitoring
- monitor blood pressure, heart rate and fluid balance.

Consensus recommendation

For people with a clear diagnosis of myocardial injury:

- seek specialist cardiology advice on treatment, further tests and imaging
- follow local treatment protocols.

Consensus recommendation

For people with a high clinical suspicion of myocardial injury, but without a clear diagnosis:

- repeat high sensitivity troponin (hs-cTnI or hs-cTnT) measurements and ECG monitoring daily, because dynamic change may help to monitor the course of the illness and establish a clear diagnosis
- seek specialist cardiology advice on further investigations such as transthoracic echocardiography and their frequency.

See also the management section for [recommendations on care planning](#) and [recommendations on escalating and de-escalating treatment](#).

Info Box

See the [Medicines and Healthcare products Regulatory Agency's Drug Safety Update on erythromycin: caution required due to cardiac risks \(QT interval prolongation\); drug interaction with rivaroxaban](#).

8.3 Venous thromboembolism (VTE) prophylaxis

Info Box

Definitions

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the [Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'](#).

Hospital-led acute care in the community: a setting in which people who would otherwise be admitted to hospital have acute medical care provided by members of the hospital team, often working with the person's GP team. They include hospital at home services and COVID-19 virtual wards.

Standard prophylactic dose: the prophylactic dose of a low molecular weight heparin (LMWH), as listed in the medicine's summary of product characteristics, for medical patients.

Intermediate dose: double the standard prophylactic dose of an LMWH for medical patients.

A treatment dose: the licensed dose of anticoagulation used to treat confirmed VTE.

8.3.1 In hospital

Consensus recommendation

For young people and adults with COVID-19 that is being managed in hospital, assess the risk of bleeding as soon as possible after admission or by the time of the first consultant review. Use a risk assessment tool published by a national UK body, professional network or peer-reviewed journal.

The [Department of Health VTE risk assessment tool](#) is commonly used to develop treatment plans.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel considered evidence from 6 trials evaluating whether higher doses (intermediate or treatment) of anticoagulation improve clinical outcomes in people in hospital with confirmed COVID-19.

Although the evidence did not show a statistically significantly increased risk of bleeding with higher doses of anticoagulation, the panel agreed that the occurrence of major bleeding events is a well-recognised adverse outcome of anticoagulant treatment. They therefore agreed that risk of bleeding should be assessed as soon as possible using a risk assessment tool to uncover any potential harm to people with a high risk.

Rationale

The panel agreed that all people with COVID-19 have an increased risk of VTE. Initial risk assessment for these people (as soon as possible after admission or by the time of their first consultant review) should focus on identifying people whose bleeding risk contraindicates pharmacological VTE prophylaxis.

The panel agreed that a risk assessment tool published by a national UK body, professional body or peer reviewed journal should be prioritised for use.

Recommended

Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and who do not have an increased bleeding risk.

Treatment should be continued for a minimum of 7 days, including after discharge.

See the [NICE recommendation on low molecular weight heparin self-administration](#).

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel agreed that a standard prophylactic dose of a low molecular weight heparin (LMWH) should be offered as soon as possible to manage the risk of VTE based on current standard practice.

The occurrence of major bleeding events is a well-recognised adverse outcome of anticoagulant treatment. The panel noted that the rate of major bleeding events reported in the studies used was relatively low for adults in hospital with moderate COVID-19 (defined in this guideline as people receiving low flow supplementary oxygen) and severe COVID-19 (defined in this guideline as people receiving high-flow oxygen). Thus the benefits of standard-dose prophylactic anticoagulation may outweigh the potential harms in these populations. The panel also noted that people who are discharged early (before 7 days) could be at risk of clots. They emphasised the importance of continuing treatment after discharge until 7 days has passed to ensure people have had a full dose of a LMWH.

The panel noted that the duration of treatment recommended in [NICE's guideline on VTE in over 16s](#) is a minimum of 7 days and thought that it would be acceptable to align treatment duration of a standard prophylactic dose of a LMWH in people with moderate or severe COVID-19 with standard practice.

Certainty of the Evidence

Moderate

The panel was presented with evidence from 3 trials (ACTION, ACTIVE-4A-ATTACC-REMAP-CAP, RAPID) that compared the effectiveness of standard-dose VTE prophylaxis with treatment-dose VTE prophylaxis. The outcomes of ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID were of moderate to very low certainty.

The panel noted that the results from RAPID were preprint results. This meant they had not been peer reviewed, so they interpreted the results with the appropriate caution. Some of the group allocated to the standard prophylactic anticoagulant dose had higher doses in the ACTION and ACTIVE-4a-ATTACC-REMAP-CAP trials (between 26% and 29%), which the panel recognised could have affected the results. However, they considered that the evidence was certain enough to make recommendations to consider standard-dose VTE prophylaxis in young people and adults with moderate or severe COVID-19.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences and values. The panel inferred that, in view of the possible mortality benefits and increase in organ support-free days for people with COVID-19 who need low-flow or high-flow oxygen, many would choose a standard dose of an anticoagulant.

Resources

No important issues with the recommended alternative

Cost effectiveness was not assessed as part of the evidence review.

The panel did not have concerns about opportunity costs when an LMWH is being used for people who need low-flow or high-flow oxygen. The panel decided to recommend that treatment is continued for up to 7 days, including after discharge. This may be a higher resource use of anticoagulation because people who are discharged before 7 days will need to learn how to self-administer LMWH at home and monitor levels.

Equity

No important issues with the recommended alternative

The panel noted an absence of evidence for anticoagulation in children. They recognised that younger children have different haematological physiology, meaning that VTE is less likely. However, their clinical experience suggested that, after puberty, people under 18 years are also at risk of VTE if admitted to hospital with COVID-19. For that reason, the panel included young people in the recommendations as well as adults.

For people under 16 years the risk of VTE is uncertain in the context of COVID-19. The risk-benefit of VTE and dosing should be discussed by multidisciplinary teams on a case-by-case basis.

Not all heparins are acceptable to people of certain religions because the products are derived from animals. The panel made a recommendation about other treatments that can be used (including fondaparinux sodium, which is not animal derived).

No other equity issues were identified at this update.

Acceptability

No important issues with the recommended alternative

It is anticipated that, when considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with COVID-19, who need low-flow or high-flow oxygen and who do not have an increased bleeding risk might favour standard-dose anticoagulation. However, we have no systematically collected evidence about acceptability.

Feasibility

No important issues with the recommended alternative

Using standard prophylactic doses in young people and adults receiving low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation reflects usual treatment in most centres. For others, it is a minor treatment adjustment that should be feasible to implement.

Rationale

The panel agreed that a standard prophylactic dose of a low molecular weight heparin (LMWH) should be offered as soon as possible to manage the risk of VTE based on current standard practice. Following standard prophylactic dose administration on admission, a more detailed assessment should be done to see whether people should be offered a treatment dose or not.

The panel also noted that people who are discharged early (before 7 days) could be at risk of clots. They emphasised the importance of continuing treatment after discharge until 7 days has passed to ensure people have had a full dose of a LMWH.

The treatment duration comes from [NICE's guideline on VTE in over 16s](#).

Clinical Question/ PICO

Population:	People with moderate COVID-19
Intervention:	Treatment dose VTE prophylaxis
Comparator:	Standard dose VTE prophylaxis

Summary

What is the evidence informing this recommendation?

Evidence comes from 3 randomised controlled trials with 3,298 participants included.

One study (ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, reported in Lawler, 2021; n=2,219) compared treatment dose anticoagulant (UFH or LMWH, mainly enoxaparin) with standard dose venous thromboembolism prophylaxis (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) according to local protocols. Treatment dose LMWH or UFH were administered according to local protocols for up to 14 days or until recovery.

In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, most of the intervention group (94.7%) received treatment dose anticoagulation, most commonly enoxaparin and in the control group 71.7% received standard prophylactic dose thromboprophylaxis and 26.5% received intermediate-dose thromboprophylaxis

The second study (ACTION trial, reported in Lopes, 2021, n=614) compared treatment dose anticoagulant (mainly rivaroxaban) for 30 days, with standard prophylactic dose anticoagulant (unfractionated heparin or enoxaparin) given whilst an inpatient and according to local hospital protocols.

Participants in the ACTION trial had a clinical 'stable' condition (93% and 95% in treatment and standard care group respectively), with a small proportion having a clinically 'unstable' condition (7% and 5% in treatment and standard care group respectively).

In the ACTION trial, most of the intervention group (94.8%) received treatment dose anticoagulation (92% rivaroxaban); stable patients were prescribed rivaroxaban 20mg once daily and clinically unstable patients SC enoxaparin 1mg/kg twice daily, or IV UFH.

Mortality and venous thromboembolism outcomes from the ACTION trial were calculated separately due to the usage of rivaroxaban as therapeutic dose anticoagulation not being standard practice in the UK.

The majority of the control group received prophylactic dose anticoagulation during hospitalisation (99.5%); unfractionated heparin/enoxaparin dosed according to local hospital protocols.

The third study (RAPID trial, reported in Sholzberg 2021, n=465) compared treatment dose anticoagulant (LMWH

and UFH) with standard dose prophylactic anticoagulant (dose-capped subcutaneous heparin (LMWH or UFH)). Study treatment was continued until the first day of hospital discharge, for 28 days or until study withdrawal/death.

The majority of participants from the RAPID trial intervention group received treatment dose heparin (98.2%) and (93.7%) received prophylactic heparin as allocated in the first 48 hours post-randomisation. Participants were moderately ill hospitalised patients with elevated D-dimer levels

Study Characteristics

The mean age in the studies ranged from 56 to 60, and between 54% and 76% of participants were male. Data for the ACTIVE-4a-ATTACC-REMAP-CAP and RAPID trials were collected from Brazil, Canada, Ireland, Netherlands, Australia, UK, Saudi Arabia, Mexico and USA. The ACTION trial was conducted in Brazil only (31 centres).

The definition of moderate severity varied between the studies. In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, moderate disease severity was defined as hospitalisation for COVID-19 without the requirement for ICU-level of care. ICU-level of care was defined by use of respiratory or cardiovascular organ support (high flow nasal oxygen, non-invasive or invasive mechanical ventilation, vasopressors, or inotropes) in an ICU. The ACTION trial defined moderate severity disease patients as those with an oxygen saturation $<94\%$, pulmonary infiltrates $<50\%$, or a partial pressure of oxygen to fractional concentration of oxygen in inspired air ratio <300 . The RAPID trial defined disease severity as hospitalised patients with elevated D-dimer levels, above the upper limit of normal (ULN) of the local hospital in the presence of an oxygen saturation of $\leq 93\%$ on room air, or ≥ 2 times the ULN irrespective of oxygen saturation levels.

The ACTION trial reported 14% of the participants were on high-flow oxygen, the rest were either on no oxygen or low-flow oxygen.

Exclusion criteria varied, but all studies excluded patients with a clinical indication for therapeutic anticoagulation and those who were at high risk of bleeding. The RAPID trial further excluded participants who were pregnant, and any participants that met any of the primary outcomes or would imminently meet them.

Duration of treatment ranged from up to 14 days (ACTIVE-4a-ATTACC-REMAP-CAP) to up to 30 days (RAPID and ACTION).

What are the main results?

Mortality at 30 days

Very low quality evidence from 2 studies found a non-statistically significant reduction in mortality at 30 days with treatment dose anticoagulant (mainly LMWH) compared with standard dose anticoagulant (UFH or LMWH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.50, CI 95% 0.13-1.88; 2,684 people in 2 studies].

Mortality at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.49, CI 95% 0.90 - 2.46; 614 people in 1 study].

All cause mortality or need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.63, CI 95% 0.39 -1.02; 465 people in 1 study].

Death or need for invasive ventilation or non-invasive ventilation or ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.75, CI 95% 0.51 – 1.11; 465 people in 1 study].

Survival

Survival to hospital discharge

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.01, CI 95% 0.99-1.03; 2,219 people in 1 study].

Survival to hospital discharge without major thrombotic events (a composite of freedom from myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, and in-hospital death)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival to hospital discharge without any macrovascular thrombotic events (the components of major thrombotic events and symptomatic deep venous thrombosis)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival without organ support 28 days

Moderate quality evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate

COVID-19 [Relative risk 1.05, CI 95% 1.01-1.10; 2,221 people in 1 study].

Organ support free days at day 21 (defined as survival to hospital discharge and, among survivors, the number of days free of ICU-level organ support through day 21)

Moderate quality evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Mean 25.8 in treatment versus 24.1 standard; CI 95% 0.32 - 3.08; 465 people in 1 study].

VTE

Venous thromboembolism at 30 days

Moderate quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.30 CI 95% 0.06 - 1.41; 465 people in 1 study].

Venous thromboembolism at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.60, CI 95% 0.29-1.24; 614 people in 1 study].

Composite Thrombotic Outcome: Any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events

Moderate quality evidence from 1 study found a non-statistically significant reduction in the composite thrombotic outcome with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.75, CI 95% 0.45-1.26; 614 people in 1 study].

ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.82, CI 95% 0.54-1.24; 465 people in 1 study].

Need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with

moderate COVID-19. [Relative risk 0.84, CI 95% 0.49-1.45; 465 people in 1 study].

Adverse events

Major bleeding was defined in both studies according to the International Society on Thrombosis and Haemostasis.

Major bleeding

Low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised with moderate COVID-19. [Relative risk 1.30, CI 95% 0.34- 4.98; 2,692 people in 2 studies].

Major bleeding - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 2.45, CI 95% 0.78-7.73; 614 people in 1 study].

Clinically relevant non-major bleeding - Rivaroxaban

Moderate quality evidence from 1 study found a statistically significant increase in clinically relevant non-major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 5.23, CI 95% 1.54-17.77; 614 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (RAPID) and two were published manuscripts (ACTION and ACTIVE-4a-ATTACC-REMAP-CAP).

Certainty of the evidence is very low for mortality at 30 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis), serious indirectness (mortality was calculated by NICE by subtracting survival from total number of events) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for mortality at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and serious imprecisions (confidence intervals cross the line of no effect).

Certainty of the evidence is moderate for all cause mortality or need for invasive ventilation and non-invasive ventilation due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for death or need for invasive ventilation or non-invasive ventilation or ICU admission due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence varies for survival outcomes.

Certainty of the evidence is low for survival to hospital discharge, survival to hospital discharge without any major thrombotic events and survival to hospital discharge without any macrovascular thrombotic events, due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and

due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for survival without organ support for 28 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis).

Certainty of the evidence is moderate for venous thromboembolism at 30 days due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for venous thromboembolism at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty if the evidence is moderate for Composite Thrombotic Outcome, due to serious imprecision (confidence interval includes the line of no effect).

Certainty of the evidence is low for major bleeding due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for clinically relevant non-major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban).

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 30 days 9 Critical	Relative risk 0.5 (CI 95% 0.13 – 1.88) Based on data from 2,684 patients in 2 studies. ¹ (Randomized controlled)	81 per 1000 Difference:	41 per 1000 41 fewer per 1000 (CI 95% 70 fewer – 71 more)	Very low Due to serious indirectness, Due to serious imprecision, Due to serious risk of bias ²	A pooled analysis of 2 studies found a non- statistically significant reduction in mortality after 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Mortality - rivaroxaban 30 days	Relative risk 1.49 (CI 95% 0.9 – 2.46) Based on data from 614	76 per 1000	113 per 1000	Low Due to serious risk of bias, Due	Evidence from 1 study found a non-statistically significant increase in

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
9 Critical	patients in 1 studies. ³ (Randomized controlled)	Difference:	37 more per 1000 (CI 95% 8 fewer – 111 more)	to serious imprecision ⁴	mortality at 30 days with treatment dose rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised
All-cause mortality or need for IV or NIV	Relative risk 0.63 (CI 95% 0.39 – 1.02) Based on data from 465 patients in 1 studies. ⁵ (Randomized controlled)	160 per 1000	101 per 1000	Moderate Due to serious imprecision ⁶	Evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
9 Critical		Difference:	59 fewer per 1000 (CI 95% 98 fewer – 3 more)		
Death / need for IV or NIV / ICU admission	Relative risk 0.75 (CI 95% 0.51 – 1.11) Based on data from 465 patients in 1 studies. ⁷ (Randomized controlled)	215 per 1000	161 per 1000	Moderate Due to serious imprecision ⁸	Evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised
9 Critical		Difference:	54 fewer per 1000 (CI 95% 105 fewer – 24 more)		
Survival to hospital discharge	Relative risk 1.01 (CI 95% 0.99 – 1.03) Based on data from 2,219 patients in 1 studies. ⁹ (Randomized controlled)	918 per 1000	927 per 1000	Low Due to serious risk of bias, Due to serious imprecision, ¹⁰	Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
9 Critical		Difference:	9 more per 1000 (CI 95% 9 fewer – 28 more)		
Survival to hospital discharge without major thrombotic events	Relative risk 1.02 (CI 95% 1 – 1.05) Based on data from 2,226 patients in 1 studies. ¹¹ (Randomized controlled)	901 per 1000	919 per 1000	Low Due to serious risk of bias, Due to serious imprecision, ¹²	Evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant compared with standard prophylactic dose anticoagulant for people who were hospitalised.
9 Critical		Difference:	18 more per 1000 (CI 95% 0 fewer – 45 more)		

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
Survival to hospital discharge without any macrovascular thrombotic events 9 Critical	Relative risk 1.02 (CI 95% 1 – 1.05) Based on data from 2,226 patients in 1 studies. ¹³ (Randomized controlled)	897 per 1000 Difference:	915 per 1000 18 more per 1000 (CI 95% 0 fewer – 45 more)	Low Due to serious risk of bias, Due to serious imprecision ¹⁴	Evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Venous thromboemboli sm 30 days 9 Critical	Relative risk 0.3 (CI 95% 0.06 – 1.41) Based on data from 465 patients in 1 studies. ¹⁵ (Randomized controlled)	30 per 1000 Difference:	9 per 1000 21 fewer per 1000 (CI 95% 28 fewer – 12 more)	Moderate Due to serious imprecision ¹⁶	Evidence from 1 study found a non- statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised. Uncertainty
Venous thromboemboli sm - rivaroxaban 30 days 9 Critical	Relative risk 0.6 (CI 95% 0.29 – 1.24) Based on data from 615 patients in 1 studies. ¹⁷ (Randomized controlled)	59 per 1000 Difference:	35 per 1000 24 fewer per 1000 (CI 95% 42 fewer – 14 more)	Low Due to serious risk of bias, Due to serious imprecision ¹⁸	Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised
Composite Thrombotic Outcome 9 Critical	Relative risk 0.75 (CI 95% 0.45 – 1.26) Based on data from 614 patients in 1 studies. ¹⁹ (Randomized controlled)	99 per 1000 Difference:	74 per 1000 25 fewer per 1000 (CI 95% 54 fewer – 26 more)	Moderate Due to serious imprecision ²⁰	Evidence from 1 study found a non-statistically significant reduction in thrombotic events (defined as any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events) with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised
Major bleeding 9 Critical	Relative risk 1.3 (CI 95% 0.34 – 4.98) Based on data from 2,692 patients in 2	10 per 1000 Difference:	13 per 1000 3 more per 1000	Low Due to serious risk of bias, Due to serious	A pooled analysis of 2 studies found a non- statistically significant increase in major

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
	studies. ²¹ (Randomized controlled)		(CI 95% 7 fewer – 40 more)	imprecision ²²	bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Major bleeding - rivaroxaban 9 Critical	Relative risk 2.45 (CI 95% 0.78 – 7.73) Based on data from 614 patients in 1 studies. ²³ (Randomized controlled)	13 per 1000 Difference:	32 per 1000 19 more per 1000 (CI 95% 3 fewer – 87 more)	Low Due to serious risk of bias, , Due to serious imprecision, ²⁴	Evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised
Survival without organ support 28 days 6 Important	Relative risk 1.3 (CI 95% 1 – 1.61) Based on data from 2,219 patients in 1 studies. ²⁵ (Randomized controlled)	754 per 1000 Difference:	980 per 1000 226 more per 1000 (CI 95% 0 fewer – 460 more)	Moderate Due to serious risk of bias, ²⁶	Evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Clinically relevant non-major bleeding - rivaroxaban 6 Important	Relative risk 5.23 (CI 95% 1.54 – 17.77) Based on data from 614 patients in 1 studies. ²⁷ (Randomized controlled)	10 per 1000 Difference:	52 per 1000 42 more per 1000 (CI 95% 5 more – 168 more)	Moderate Due to serious risk of bias, ²⁸	Evidence from 1 study found a statistically significant increase in clinically relevant non-major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
ICU admission 6 Important	Relative risk 0.82 (CI 95% 0.54 – 1.24) Based on data from 465 patients in 1 studies. ²⁹ (Randomized controlled)	177 per 1000 Difference:	145 per 1000 32 fewer per 1000 (CI 95% 81 fewer – 42 more)	Moderate Due to serious imprecision ³⁰	Evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Need for IV or NIV 6 Important	Relative risk 0.84 (CI 95% 0.49 – 1.45) Based on data from 465 patients in 1 studies. ³¹ (Randomized controlled)	110 per 1000 Difference:	92 per 1000 18 fewer per	Moderate Due to serious imprecision ³²	Evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
			1000 (CI 95% 56 fewer – 50 more)		invasive ventilation with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Organ support- free days	Based on data from: 465 patients in 1 studies. ³³ (Randomized controlled)	24.1 (Mean)	25.8 (Mean)	Moderate Due to serious risk of bias ³⁴	Evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
6 Important		Difference:	MD 1.7 higher (CI 95% 0.32 higher – 3.08 higher)		

1. Systematic review [84] with included studies: REMAP-CAP 2021, RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: serious.** Mortality in REMAP-CAP was calculated by NICE (through subtracting no. survival until discharge from total no. of events). **Imprecision: serious.** 95% CI crossed line of no effect. **Publication bias: no serious.**
3. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Small number of participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
5. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
7. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
9. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses line of no effect. **Publication bias: no serious.**
11. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed line of no effect. **Publication bias: no serious.**
13. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis,

71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis).

Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. 95% CI crossed the line of no effect.

Publication bias: no serious.

15. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect.

Publication bias: no serious.

17. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Risk of Bias: serious.** Due to study design where participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious.**

Imprecision: serious. CI included line of no effect. **Publication bias: no serious.**

19. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.

20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% confidence interval crossed the line of no effect.. **Publication bias: no serious.**

21. Systematic review [82] with included studies: REMAP-CAP 2021, RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

22. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis).

Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Wide confidence intervals. **Publication bias: no serious.**

23. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.

24. **Risk of Bias: serious.** Participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed line of effect. **Publication bias: no serious.**

25. Systematic review [82] with included studies: [85]. **Baseline/comparator:** Control arm of reference used for intervention.

26. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis).

Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.

27. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.

28. **Risk of Bias: serious.** 13% were prescribed treatment beyond hospital discharge. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

29. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

30. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect.

Publication bias: no serious.

31. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

32. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect.

Publication bias: no serious.

33. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

34. **Risk of Bias: serious.** participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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Clinical Question/ PICO

Population: People with severe COVID-19
Intervention: Treatment dose VTE prophylaxis
Comparator: Standard dose VTE prophylaxis

Summary

What is the evidence informing this recommendation?

Evidence comes from 2 randomised controlled trials with 1,089 participants included. Both studies (HESACOVID trial, reported in Lemos, 2020, n=20; and ACTIVE-41, ATACC, REMAP-CAP multiplatform trial, reported in Lawler, 2021, n=1,098) compared treatment dose anticoagulant (unfractionated heparin (UFH) or low molecular weight heparin (LMWH)) with either prophylactic or intermediate dose anticoagulant (mainly enoxaparin).

The comparator group varies between studies. In the HESACOVID trial, half of the comparator group received UFH and half received prophylactic dose enoxaparin. The ACTIVE-41, ATACC, REMAP-CAP trial combines data from three sites, each operating under their own protocols. The protocols are very similar but allow for local practice, meaning that just over 40% of the comparator arm received prophylactic dose enoxaparin, just over 50% received intermediate dose enoxaparin, and 7.4% received either subtherapeutic (dose unclear) or therapeutic dose of either UFH or LMWH. This may reduce the validity of the results from the ACTIVE-41, ATACC, REMAP-CAP trial.

Study characteristics

The mean age in the studies ranged from 55 to 61, and between 68% and 90% of participants were male. Both studies included only adult patients receiving intensive care unit-level respiratory or cardiovascular support. Data was collected from Australia, Brazil, Canada, Ireland, Mexico, Netherlands, New Zealand, Saudi Arabia, UK, and USA.

Exclusion criteria varied, but both studies excluded patients with a separate clinical indication for therapeutic anticoagulation. One study excluded patients over 85.

Duration of treatment was 4-14 days in HESACOVID, and up to 14 days or hospital discharge in ACTIVE-41, ATACC, REMAP-CAP.

What are the main results?

All-cause mortality

Very low quality evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (LMWH or UFH) compared to either prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised. [Relative risk 0.33 CI 95% 0.04 - 2.69; 20 people in 1 study].

Death in hospital

Low quality evidence from a pooled analysis of 2 studies found no significant difference for death in hospital with treatment dose anticoagulant (LMWH at varying doses) compared with either UFH, enoxaparin or usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 1.03, CI 95% 0.89-1.21; 1,118 people in 2 studies].

Survival to hospital discharge

Low quality evidence from 1 study found no significant difference for survival to hospital discharge with treatment dose anticoagulant compared with usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 0.97, CI 95% 0.89-1.06; 1,098 people in 1 study].

Serious Adverse events: Major bleeding

Low quality evidence from a pooled analysis of 2 studies found no significant difference in major bleeding with treatment dose anticoagulant compared with prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised. [Relative risk 1.63, CI 95% 0.82 - 3.25; 1,111 people in 2 studies].

Organ-support free days at 21 days

Low quality evidence from 1 study found no statistically significant difference in organ-support free days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Odds Ratio 0.83, CI 95% 0.67 - 1.03; 1,098 people in 1 study].

Ventilator-free days

Low quality evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 15 versus 0; 20 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. The two studies were published manuscripts (ACTIVE-41, ATACC, REMAP-CAP and HESACOVID). Following the peer reviewed publication of ACTIVE-41, ATACC, REMAP-CAP (26/08/2021), the data for some of the outcomes was updated to reflect the latest figures in the published manuscript.

There were significant deviations from the intended interventions reported in one study (ACTIVE-41, ATACC, REMAP-CAP) whereby a large proportion of the comparator group received intermediate rather than prophylactic dose anticoagulant. In addition, almost 15% of the treatment group received either low or intermediate dose anticoagulant, where the intended intervention was treatment dose anticoagulant. This means the results from this study are unclear.

One study (HESACOVID) contained only 20 participants (10 in each arm). This trial did not have sufficient power to assess a difference in mortality, and results may be due to chance. This should be considered when looking at the increase in ventilator free days in the treatment group reported by this study.

Certainty of the evidence is very low for all-cause mortality due to serious risk of bias (deviation from intended control group treatment) and very serious imprecision (confidence intervals include the line of no effect and low numbers of participants).

Certainty of the evidence is low for death in hospital due to serious risk of bias, serious inconsistency (high statistical heterogeneity) and serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for survival to hospital discharge due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for major bleeding due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for organ support free days due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for ventilator-free days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals).

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality 28 days 9 Critical	Relative risk 0.33 (CI 95% 0.04 – 2.69) Based on data from 20 patients in 1 studies. ¹ (Randomized controlled)	300 per 1000 Difference:	99 per 1000 201 fewer per 1000 (CI 95% 288 fewer – 507 more)	Very low Due to serious risk of bias and very serious imprecision ²	Evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (unfractionated heparin or low molecular weight heparin) compared to either standard prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised.
Death in hospital 9 Critical	Relative risk 1.03 (CI 95% 0.89 – 1.21) Based on data from 1,118 patients in 2 studies. ³ (Randomized controlled)	357 per 1000 Difference:	368 per 1000 11 more per 1000 (CI 95% 39 fewer – 75 more)	Low Due to serious risk of bias, Due to serious imprecision ⁴	A pooled analysis of 2 studies found no statistically significant difference in death in hospital with treatment dose anticoagulant (low molecular weight heparin at varying doses) compared to either unfractionated heparin, enoxaparin or standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.
Survival to hospital discharge 9 Critical	Relative risk 0.97 (CI 95% 0.89 – 1.06) Based on data from 1,098 patients in 1 studies. ⁵ (Randomized controlled)	645 per 1000 Difference:	626 per 1000 19 fewer per 1000 (CI 95% 71 fewer – 39 more)	Low Due to serious risk of bias, Due to serious imprecision ⁶	Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
					(dose and treatment varies) for people who were hospitalised.
Major bleeding 9 Critical	Relative risk 1.63 (CI 95% 0.82 – 3.25) Based on data from 1,111 patients in 2 studies. ⁷ (Randomized controlled)	23 per 1000 Difference:	37 per 1000 14 more per 1000 (CI 95% 4 fewer – 52 more)	Low Due to serious risk of bias, Due to serious imprecision ⁸	A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.
Organ support free days 21 days 6 Important	Odds Ratio 0.83 (CI 95% 0.67 – 1.03) Based on data from 1,098 patients in 1 studies. (Randomized controlled)	567 per 1000 Difference:	536 per 1000 46 fewer per 1000 (CI 95% 100 fewer – 7 more)	Low Due to serious risk of bias, Due to serious imprecision ⁹	Evidence from 1 study found no statistically significant difference in organ support free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Ventilator-free days 28 days 6 Important	High better Based on data from: 20 patients in 1 studies. (Randomized controlled)	0 (Median)	15 (Median) CI 95%	Low Due to very serious imprecision ¹⁰	Evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

1. Systematic review [78] with included studies: HESACOVID 2020, HESACOVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis, due to [reason]. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No statistically significant effect, and low number of patients., due to [reason]. **Publication bias: no serious.**
3. Systematic review [93] with included studies: REMAP-CAP 2021, HESACOVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
5. Systematic review [93] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
7. Systematic review [93] with included studies: REMAP-CAP 2021, HESACOVID 2020. **Baseline/comparator:** Control

arm of reference used for intervention.

8. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**

9. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI includes line of no effect. **Publication bias: no serious.**

10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Unable to calculate effect size and 95% C.I.. **Publication bias: no serious.**

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Clinical Question/ PICO

Population:	People with severe COVID-19
Intervention:	Intermediate dose VTE prophylaxis
Comparator:	Standard dose VTE prophylaxis

Summary

What is the evidence informing this recommendation?

Evidence comes from 2 randomised controlled trials with 735 participants included. Both studies (INSPIRATION trial, reported in Sadeghipour 2021 [for 30 day outcomes] and Bikdeli, 2021 [for 90 day outcomes], n=562 and Perepu 2021 n=173) compared intermediate dose enoxaparin (1mg/kg daily if the BMI was <30 or 0.5 mg/kg SC twice daily if the BMI was ≥30) with prophylactic dose enoxaparin (40mg daily).

The intervention and comparator groups were consistent between the studies. However, Perepu (2021) allowed for cointerventions, and more patients received azithromycin in the intermediate dose arm (29%) than in the prophylactic dose arm (13%).

Study characteristics

The mean age in the studies ranged from 61 to 65, and between 56% and 58% of participants were male. Both studies investigate the effects of the interventions in severe patients, but approximately 45% of the participants in the INSPIRATION trial were receiving low-flow oxygen and would therefore not be classed as having severe COVID-19 by the definitions used in the study protocol. The proportion of participants in Perepu (2021) receiving low-flow oxygen is unclear: it is reported that 62% were admitted to intensive care and 23% received invasive mechanical ventilation.

Data was collected from IRAN (INSPIRATION trial) and the USA (Perepu 2021).. Participants were excluded if they

had recent known major bleeding or indications for a therapeutic dose of anticoagulant. Both studies excluded pregnant women. Duration of treatment was until hospital discharge (Perepu 2021) or for 30 and 90 days (INSPIRATION).

What are the main results?

All-cause mortality

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.01, CI 95% 0.84– 1.21; 735 people in 2 studies].

Low quality evidence from 1 study found no significant difference for all-cause mortality at 90 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.07, CI 95% 0.89 - 1.29; 562 people in 1 study]

Serious Adverse events: Major bleeding

Very low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with intermediate dose anticoagulant compared to prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised. [Relative risk 1.53, CI 95% 0.54 -4.28; 735 people in 2 studies]

Venous thromboembolism

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.02, CI 95% 0.52 – 2.00; 735 people in 2 studies]

Low quality evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 0.93, CI 95% 0.38 – 2.26; 562 people in 1 study]

Ventilator-free days

Very low quality evidence from 1 study found no significant difference for ventilator-free days at 30 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 30 days in intermediate dose group versus 30 days in prophylactic dose group; 562 people in 1 study].

Our confidence in the results

Both studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (Perepu, 21). The other study was from published manuscripts that reported 30 day and 90 day outcomes separately (INSPIRATION 2021).

Certainty of the evidence is low or very low for mortality outcomes due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for major bleeding due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe

COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for VTE outcomes at 30 days due to serious risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for VTE outcomes at 90 days to serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of evidence is very low for ventilator-free days at 30 days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals) and serious indirectness (dissimilarity between population of interest and those studied).

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Intermediate dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality 30 days 9 Critical	Relative risk 1.01 (CI 95% 0.84 – 1.21) Based on data from 735 patients in 2 studies. ¹ (Randomized controlled)	363 per 1000 Difference:	367 per 1000 4 more per 1000 (CI 95% 58 fewer – 76 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision ²	A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
All-cause mortality 90 days 9 Critical	Relative risk 1.07 (CI 95% 0.89 – 1.29) Based on data from 562 patients in 1 studies. ³ (Randomized controlled)	430 per 1000 Difference:	460 per 1000 30 more per 1000 (CI 95% 47 fewer – 125 more)	Low Due to serious indirectness and serious imprecision ⁴	Evidence from 1 study found no statistically significant difference in all-cause mortality at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Major bleeding 9 Critical	Relative risk 1.53 (CI 95% 0.54 – 4.28) Based on data from 735 patients in 2 studies. ⁵ (Randomized controlled)	16 per 1000 Difference:	24 per 1000 8 more per 1000 (CI 95% 7 fewer – 52 more)	Very low Due to serious risk of bias, serious indirectness and serious imprecision ⁶	A pooled analysis of 2 studies found a non- statistically significant increase in major bleeding with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised.

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Intermediate dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
VTE 30 days 9 Critical	Relative risk 1.02 (CI 95% 0.52 – 2) Based on data from 735 patients in 2 studies. ⁷ (Randomized controlled)	43 per 1000 Difference:	44 per 1000 1 more per 1000 (CI 95% 21 fewer – 43 more)	Very low Due to serious risk of bias, serious indirectness and serious imprecision ⁸	A pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
VTE 90 days 9 Critical	Relative risk 0.93 (CI 95% 0.38 – 2.26) Based on data from 562 patients in 1 studies. ⁹ (Randomized controlled)	35 per 1000 Difference:	33 per 1000 2 fewer per 1000 (CI 95% 22 fewer – 44 more)	Low Due to serious indirectness and serious imprecision ¹⁰	Evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Ventilator-free days 30 days 6 Important	High better Based on data from: 562 patients in 1 studies. (Randomized controlled)	30 (Median)	30 (Median) CI 95%	Very low Due to serious indirectness and very serious imprecision ¹¹	Evidence from 1 study found no statistically significant difference in ventilator-free days at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

1. Systematic review [83] with included studies: INSPIRATION 2021, Perepu 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients have moderate in one study have moderate, not severe COVID-19. **Imprecision: serious.** No statistically significant effect. **Publication bias: no serious.**
3. Systematic review [79] with included studies: INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
5. Systematic review [79] with included studies: INSPIRATION 2021, Perepu 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients in one study have moderate, not severe COVID-19.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
7. Systematic review [79] with included studies: INSPIRATION 2021, Perepu 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients in one study have moderate, not severe COVID-19.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
9. Systematic review [79] with included studies: INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.

10. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
11. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied.. **Imprecision: very serious.** Unable to calculate effect size and 95% C.I.. **Publication bias: no serious.**

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Conditional recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk.

Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances.

For people with COVID-19 who do not need low-flow oxygen, follow the [recommendations in NICE's guideline on venous thromboembolism in over 16s](#).

In August 2021, using a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. See [NICE's information on prescribing medicines](#).

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel were presented with data from 3 randomised controlled trials (ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID). These trials evaluated whether empiric use of treatment-dose anticoagulation improves clinical outcomes in adults in hospital with confirmed moderate COVID-19 (defined in this guideline as people receiving low-flow supplementary oxygen).

The panel agreed that, for adults with moderate COVID-19, the studies showed a trend towards improved mortality outcomes with a treatment dose of an anticoagulant compared with the standard prophylactic dose. One study reported no difference in survival to hospital discharge and a statistically significant increase in survival without organ support at 28 days. The panel also emphasised a trend towards a positive effect on VTE at 30 and 90 days, and a statistically significant increase in organ-support-free days.

The occurrence of major bleeding events is a well-recognised adverse outcome of anticoagulant treatment. The panel noted that the rate of major bleeding events was relatively low for adults in hospital with moderate COVID-19. Thus the benefits of treatment-dose prophylactic anticoagulation may outweigh the potential harms in this population.

The panel noted that the duration of treatment recommended should match the duration of the largest study included,

which was 14 days or until discharge, whichever was sooner.

Certainty of the Evidence

Moderate

The outcomes of ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID were of moderate to very low certainty.

The panel noted that the results from RAPID were preprint results. This meant they had not been peer reviewed, so they interpreted the results with the appropriate caution. Some of the group allocated to the standard prophylactic anticoagulant dose had higher doses in the ACTION and ACTIVE-4a-ATTACC-REMAP-CAP trials (between 26% and 29%), which the panel recognised could have affected the results. However, they considered that the evidence was certain enough to make recommendations to consider treatment-dose VTE prophylaxis in young people and adults with moderate COVID-19.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences and values. The panel inferred that, in view of the possible mortality benefits and increase in organ support-free days for people with COVID-19 who need low-flow oxygen, many would choose a treatment dose of an anticoagulant in spite of a potential increased risk of bleeding.

Resources

No important issues with the recommended alternative

Cost effectiveness was not assessed as part of the evidence review.

The panel did not have concerns about opportunity costs when a low molecular weight heparin is being used for people who need low-flow oxygen. The panel decided to recommend that treatment is continued for up to 14 days. This may be longer than the standard treatment duration for acute illness (at least 7 days), so may be a higher resource use of anticoagulation in this group. This is to reflect the duration used in the trials contributing evidence to this recommendation.

Equity

No important issues with the recommended alternative

The panel noted an absence of evidence for anticoagulation in children. They recognised that younger children have different haematological physiology, meaning that VTE is less likely. However, their clinical experience suggested that, after puberty, people under 18 years are also at risk of VTE if admitted to hospital with COVID-19. For that reason, the panel included young people in the recommendations as well as adults. Additionally, a research recommendation was made for this population.

For people under 16 years the risk of VTE is uncertain in the context of COVID-19. The risk benefit of VTE and dosing should be discussed by multidisciplinary teams on a case-by-case basis.

Not all heparins are acceptable to people of certain religions because the products are derived from animals. The panel made a recommendation about other treatments that can be used (including fondaparinux sodium, which is not animal derived).

No other equity issues were identified at this update.

Acceptability

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about acceptability. A potential deterring factor to acceptability could be that the certainty of current evidence is only moderate to very low. However, the panel noted that the direction of effect tended to favour treatment-dose anticoagulation for adults with COVID-19 who need low-flow supplemental oxygen.

It is anticipated that, when considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with COVID-19, who need low-flow oxygen and who do not have an increased bleeding risk might favour treatment-dose anticoagulation.

Feasibility

No important issues with the recommended alternative

Implementing use of treatment-dose VTE prophylaxis in young people and adults in hospital who are receiving low-flow oxygen is expected to be feasible because it represents an increase in the dose and duration of an established treatment.

Rationale

The panel agreed that some young people and adults with COVID-19 who need low-flow oxygen supplementation may benefit from a treatment dose of a low molecular weight heparin (LMWH). The evidence suggests that a treatment dose of an LMWH for adults with COVID-19 who are in hospital and needing low-flow oxygen supplementation may reduce the risk of death and need for organ support compared with a standard prophylactic dose. It also suggests an increased risk in major bleeding compared with a standard prophylactic dose. Because of the fine balance of benefits and harms, the panel agreed that this decision should be carefully considered, and that this choice should be guided by bleeding risk, clinical judgement and local protocols.

The treatment duration in the largest included trial was 14 days or until discharge, whichever was sooner. The panel thought that the timeframe for treatment should reflect the trial evidence.

Clinical Question/ PICO

Population: People with moderate COVID-19

Intervention: Treatment dose VTE prophylaxis

Comparator: Standard dose VTE prophylaxis

Summary

What is the evidence informing this recommendation?

Evidence comes from 3 randomised controlled trials with 3,298 participants included.

One study (ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, reported in Lawler, 2021; n=2,219) compared treatment dose anticoagulant (UFH or LMWH, mainly enoxaparin) with standard dose venous thromboembolism prophylaxis (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) according to local protocols. Treatment dose LMWH or UFH were administered according to local protocols for up to 14 days or until recovery.

In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, most of the intervention group (94.7%) received treatment dose anticoagulation, most commonly enoxaparin and in the control group 71.7% received standard prophylactic dose thromboprophylaxis and 26.5% received intermediate-dose thromboprophylaxis

The second study (ACTION trial, reported in Lopes, 2021, n=614) compared treatment dose anticoagulant (mainly rivaroxaban) for 30 days, with standard prophylactic dose anticoagulant (unfractionated heparin or enoxaparin) given whilst an inpatient and according to local hospital protocols.

Participants in the ACTION trial had a clinical 'stable' condition (93% and 95% in treatment and standard care group respectively), with a small proportion having a clinically 'unstable' condition (7% and 5% in treatment and standard care group respectively).

In the ACTION trial, most of the intervention group (94.8%) received treatment dose anticoagulation (92% rivaroxaban); stable patients were prescribed rivaroxaban 20mg once daily and clinically unstable patients SC enoxaparin 1mg/kg twice daily, or IV UFH.

Mortality and venous thromboembolism outcomes from the ACTION trial were calculated separately due to the usage of rivaroxaban as therapeutic dose anticoagulation not being standard practice in the UK.

The majority of the control group received prophylactic dose anticoagulation during hospitalisation (99.5%); unfractionated heparin/enoxaparin dosed according to local hospital protocols.

The third study (RAPID trial, reported in Sholzberg 2021, n=465) compared treatment dose anticoagulant (LMWH and UFH) with standard dose prophylactic anticoagulant (dose-capped subcutaneous heparin (LMWH or UFH)). Study treatment was continued until the first day of hospital discharge, for 28 days or until study withdrawal/death.

The majority of participants from the RAPID trial intervention group received treatment dose heparin (98.2%) and (93.7%) received prophylactic heparin as allocated in the first 48 hours post-randomisation. Participants were moderately ill hospitalised patients with elevated D-dimer levels

Study Characteristics

The mean age in the studies ranged from 56 to 60, and between 54% and 76% of participants were male. Data for the ACTIVE-4a-ATTACC-REMAP-CAP and RAPID trials were collected from Brazil, Canada, Ireland, Netherlands, Australia, UK, Saudi Arabia, Mexico and USA. The ACTION trial was conducted in Brazil only (31 centres).

The definition of moderate severity varied between the studies. In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, moderate disease severity was defined as hospitalisation for COVID-19 without the requirement for ICU-level of care. ICU-level of care was defined by use of respiratory or cardiovascular organ support (high flow nasal oxygen, non-invasive or invasive mechanical ventilation, vasopressors, or inotropes) in an ICU. The ACTION trial defined moderate severity disease patients as those with an oxygen saturation <94%, pulmonary infiltrates <50%, or a partial pressure of oxygen to fractional concentration of oxygen in inspired air ratio <300. The RAPID trial defined disease severity as hospitalised patients with elevated D-dimer levels, above the upper limit of normal (ULN) of the local hospital in the presence of an oxygen saturation of $\leq 93\%$ on room air, or ≥ 2 times the ULN irrespective of oxygen saturation levels.

The ACTION trial reported 14% of the participants were on high-flow oxygen, the rest were either on no oxygen or low-flow oxygen.

Exclusion criteria varied, but all studies excluded patients with a clinical indication for therapeutic anticoagulation and those who were at high risk of bleeding. The RAPID trial further excluded participants who were pregnant, and any participants that met any of the primary outcomes or would imminently meet them.

Duration of treatment ranged from up to 14 days (ACTIVE-4a-ATTACC-REMAP-CAP) to up to 30 days (RAPID and ACTION).

What are the main results?

Mortality at 30 days

Very low quality evidence from 2 studies found a non-statistically significant reduction in mortality at 30 days with treatment dose anticoagulant (mainly LMWH) compared with standard dose anticoagulant (UFH or LMWH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.50, CI 95% 0.13-1.88; 2,684 people in 2 studies].

Mortality at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.49, CI 95% 0.90 - 2.46; 614 people in 1 study].

All cause mortality or need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.63, CI 95% 0.39 - 1.02; 465 people in 1 study].

Death or need for invasive ventilation or non-invasive ventilation or ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.75, CI 95% 0.51 - 1.11; 465 people in 1 study].

Survival

Survival to hospital discharge

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.01, CI 95% 0.99-1.03; 2,219 people in 1 study].

Survival to hospital discharge without major thrombotic events (a composite of freedom from myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, and in-hospital death)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival to hospital discharge without any macrovascular thrombotic events (the components of major thrombotic events and symptomatic deep venous thrombosis)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival without organ support 28 days

Moderate quality evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.05, CI 95% 1.01-1.10; 2,221 people in 1 study].

Organ support free days at day 21 (defined as survival to hospital discharge and, among survivors, the number of days free of ICU-level organ support through day 21)

Moderate quality evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Mean 25.8 in treatment versus 24.1 standard; CI 95% 0.32 - 3.08; 465 people in 1 study].

VTE

Venous thromboembolism at 30 days

Moderate quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.30 CI 95% 0.06 - 1.41; 465 people in 1 study].

Venous thromboembolism at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.60, CI 95% 0.29-1.24; 614 people in 1 study].

Composite Thrombotic Outcome: Any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events

Moderate quality evidence from 1 study found a non-statistically significant reduction in the composite thrombotic outcome with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or

enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.75, CI 95% 0.45-1.26; 614 people in 1 study].

ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.82, CI 95% 0.54-1.24; 465 people in 1 study].

Need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.84, CI 95% 0.49-1.45; 465 people in 1 study].

Adverse events

Major bleeding was defined in both studies according to the International Society on Thrombosis and Haemostasis.

Major bleeding

Low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised with moderate COVID-19. [Relative risk 1.30, CI 95% 0.34- 4.98; 2,692 people in 2 studies].

Major bleeding - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 2.45, CI 95% 0.78-7.73; 614 people in 1 study].

Clinically relevant non-major bleeding - Rivaroxaban

Moderate quality evidence from 1 study found a statistically significant increase in clinically relevant non-major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 5.23, CI 95% 1.54-17.77; 614 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (RAPID) and two were published manuscripts (ACTION and ACTIVE-4a-ATTACC-REMAP-CAP).

Certainty of the evidence is very low for mortality at 30 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis), serious indirectness (mortality was calculated by NICE by subtracting survival from total number of events) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for mortality at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and serious imprecisions (confidence intervals cross the line of no effect).

Certainty of the evidence is moderate for all cause mortality or need for invasive ventilation and non-invasive ventilation due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for death or need for invasive ventilation or non-invasive ventilation or ICU admission due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence varies for survival outcomes.

Certainty of the evidence is low for survival to hospital discharge, survival to hospital discharge without any major thrombotic events and survival to hospital discharge without any macrovascular thrombotic events, due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for survival without organ support for 28 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis).

Certainty of the evidence is moderate for venous thromboembolism at 30 days due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for venous thromboembolism at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty if the evidence is moderate for Composite Thrombotic Outcome, due to serious imprecision (confidence interval includes the line of no effect).

Certainty of the evidence is low for major bleeding due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for clinically relevant non-major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban).

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 30 days 9 Critical	Relative risk 0.5 (CI 95% 0.13 – 1.88) Based on data from 2,684 patients in 2 studies. ¹ (Randomized controlled)	81 per 1000 Difference:	41 per 1000 41 fewer per 1000 (CI 95% 70 fewer – 71 more)	Very low Due to serious indirectness, Due to serious imprecision, Due to serious risk of bias ²	A pooled analysis of 2 studies found a non- statistically significant reduction in mortality after 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Mortality - rivaroxaban 30 days 9 Critical	Relative risk 1.49 (CI 95% 0.9 – 2.46) Based on data from 614 patients in 1 studies. ³ (Randomized controlled)	76 per 1000 Difference:	113 per 1000 37 more per 1000 (CI 95% 8 fewer – 111 more)	Low Due to serious risk of bias, Due to serious imprecision ⁴	Evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised
All-cause mortality or need for IV or NIV 9 Critical	Relative risk 0.63 (CI 95% 0.39 – 1.02) Based on data from 465 patients in 1 studies. ⁵ (Randomized controlled)	160 per 1000 Difference:	101 per 1000 59 fewer per 1000 (CI 95% 98 fewer – 3 more)	Moderate Due to serious imprecision ⁶	Evidence from 1 study found a non- statistically significant reduction in all cause mortality and need for ventilation with with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Death / need for IV or NIV / ICU admission 9 Critical	Relative risk 0.75 (CI 95% 0.51 – 1.11) Based on data from 465 patients in 1 studies. ⁷ (Randomized controlled)	215 per 1000 Difference:	161 per 1000 54 fewer per 1000 (CI 95% 105 fewer – 24 more)	Moderate Due to serious imprecision ⁸	Evidence from 1 study found a non- statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised
Survival to hospital discharge 9 Critical	Relative risk 1.01 (CI 95% 0.99 – 1.03) Based on data from 2,219 patients in 1 studies. ⁹ (Randomized controlled)	918 per 1000 Difference:	927 per 1000 9 more per 1000 (CI 95% 9 fewer – 28 more)	Low Due to serious risk of bias, Due to serious imprecision, ¹⁰	Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
					hospitalised.
Survival to hospital discharge without major thrombotic events 9 Critical	Relative risk 1.02 (CI 95% 1 – 1.05) Based on data from 2,226 patients in 1 studies. ¹¹ (Randomized controlled)	901 per 1000 Difference:	919 per 1000 18 more per 1000 (CI 95% 0 fewer – 45 more)	Low Due to serious risk of bias, Due to serious imprecision, ¹²	Evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant compared with standard prophylactic dose anticoagulant for people who were hospitalised.
Survival to hospital discharge without any macrovascular thrombotic events 9 Critical	Relative risk 1.02 (CI 95% 1 – 1.05) Based on data from 2,226 patients in 1 studies. ¹³ (Randomized controlled)	897 per 1000 Difference:	915 per 1000 18 more per 1000 (CI 95% 0 fewer – 45 more)	Low Due to serious risk of bias, Due to serious imprecision ¹⁴	Evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Venous thromboemboli sm 30 days 9 Critical	Relative risk 0.3 (CI 95% 0.06 – 1.41) Based on data from 465 patients in 1 studies. ¹⁵ (Randomized controlled)	30 per 1000 Difference:	9 per 1000 21 fewer per 1000 (CI 95% 28 fewer – 12 more)	Moderate Due to serious imprecision ¹⁶	Evidence from 1 study found a non- statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised. Uncertainty
Venous thromboemboli sm - rivaroxaban 30 days 9 Critical	Relative risk 0.6 (CI 95% 0.29 – 1.24) Based on data from 615 patients in 1 studies. ¹⁷ (Randomized controlled)	59 per 1000 Difference:	35 per 1000 24 fewer per 1000 (CI 95% 42 fewer – 14 more)	Low Due to serious risk of bias, Due to serious imprecision ¹⁸	Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised
Composite Thrombotic Outcome	Relative risk 0.75 (CI 95% 0.45 – 1.26) Based on data from 614 patients in 1 studies. ¹⁹ (Randomized controlled)	99 per 1000 Difference:	74 per 1000 25 fewer per	Moderate Due to serious imprecision ²⁰	Evidence from 1 study found a non-statistically significant reduction in thrombotic events (defined as any venous

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
			1000 (CI 95% 54 fewer – 26 more)		thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events) with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised
9 Critical					
Major bleeding	Relative risk 1.3 (CI 95% 0.34 – 4.98) Based on data from 2,692 patients in 2 studies. ²¹ (Randomized controlled)	10 per 1000 Difference:	13 per 1000 3 more per 1000 (CI 95% 7 fewer – 40 more)	Low Due to serious risk of bias, Due to serious imprecision ²²	A pooled analysis of 2 studies found a non- statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
9 Critical					
Major bleeding - rivaroxaban	Relative risk 2.45 (CI 95% 0.78 – 7.73) Based on data from 614 patients in 1 studies. ²³ (Randomized controlled)	13 per 1000 Difference:	32 per 1000 19 more per 1000 (CI 95% 3 fewer – 87 more)	Low Due to serious risk of bias, , Due to serious imprecision, ²⁴	Evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised
9 Critical					
Survival without organ support 28 days	Relative risk 1.3 (CI 95% 1 – 1.61) Based on data from 2,219 patients in 1 studies. ²⁵ (Randomized controlled)	754 per 1000 Difference:	980 per 1000 226 more per 1000 (CI 95% 0 fewer – 460 more)	Moderate Due to serious risk of bias, ²⁶	Evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
6 Important					
Clinically relevant non- major bleeding - rivaroxaban	Relative risk 5.23 (CI 95% 1.54 – 17.77) Based on data from 614 patients in 1 studies. ²⁷ (Randomized controlled)	10 per 1000 Difference:	52 per 1000 42 more per 1000 (CI 95% 5 more – 168 more)	Moderate Due to serious risk of bias, ²⁸	Evidence from 1 study found a statistically significant increase in clinically relevant non- major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
6 Important					

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
ICU admission 6 Important	Relative risk 0.82 (CI 95% 0.54 – 1.24) Based on data from 465 patients in 1 studies. ²⁹ (Randomized controlled)	177 per 1000 Difference:	145 per 1000 32 fewer per 1000 (CI 95% 81 fewer – 42 more)	Moderate Due to serious imprecision ³⁰	Evidence from 1 study found a non- statistically significant reduction in ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Need for IV or NIV 6 Important	Relative risk 0.84 (CI 95% 0.49 – 1.45) Based on data from 465 patients in 1 studies. ³¹ (Randomized controlled)	110 per 1000 Difference:	92 per 1000 18 fewer per 1000 (CI 95% 56 fewer – 50 more)	Moderate Due to serious imprecision ³²	Evidence from 1 study found no statistically significant difference in need for invasive ventilation or non- invasive ventilation with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Organ support- free days 6 Important	Based on data from: 465 patients in 1 studies. ³³ (Randomized controlled)	24.1 (Mean) Difference:	25.8 (Mean) MD 1.7 higher (CI 95% 0.32 higher – 3.08 higher)	Moderate Due to serious risk of bias ³⁴	Evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

1. Systematic review [84] with included studies: REMAP-CAP 2021, RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: serious.** Mortality in REMAP-CAP was calculated by NICE (through subtracting no. survival until discharge from total no. of events). **Imprecision: serious.** 95% CI crossed line of no effect. **Publication bias: no serious.**
3. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Small number of participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
5. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
7. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
9. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference

used for intervention.

10. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis).

Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. 95% CI crosses line of no effect. **Publication bias: no serious.**

11. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.

12. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis).

Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. 95% CI crossed line of no effect. **Publication bias: no serious.**

13. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.

14. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis).

Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. 95% CI crossed the line of no effect.

Publication bias: no serious.

15. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect.

Publication bias: no serious.

17. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Risk of Bias: serious.** Due to study design where participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious.**

Imprecision: serious. CI included line of no effect. **Publication bias: no serious.**

19. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.

20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% confidence interval crossed the line of no effect.. **Publication bias: no serious.**

21. Systematic review [82] with included studies: REMAP-CAP 2021, RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

22. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis).

Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Wide confidence intervals. **Publication bias: no serious.**

23. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.

24. **Risk of Bias: serious.** Participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed line of effect. **Publication bias: no serious.**

25. Systematic review [82] with included studies: [85]. **Baseline/comparator:** Control arm of reference used for intervention.

26. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis).

Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.

27. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.

28. **Risk of Bias: serious.** 13% were prescribed treatment beyond hospital discharge. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

29. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

30. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**

31. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

32. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect.

Publication bias: no serious.

33. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

34. **Risk of Bias: serious.** participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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Only in research settings

Only offer an intermediate or treatment dose of a low molecular weight heparin to young people and adults with COVID-19 who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation as part of a clinical trial.

Evidence To Decision**Benefits and harms**

Small net benefit, or little difference between alternatives

The panel were presented with data from 4 open-label randomised controlled trials (INSPIRATION, ATTACC, ACTIV-4a, REMAP-CAP, HESACOVID and Perepu [2021]). These trials evaluated the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults having care for severe COVID-19 (that is, receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation).

Intermediate-dose anticoagulant

Two studies compared intermediate-dose anticoagulation with the standard prophylactic dose (INSPIRATION and Perepu [2021]). The panel agreed that, for adults with severe COVID-19, the studies showed no statistically significant benefit for mortality, VTE prophylaxis or ventilator-free days with an intermediate dose of an anticoagulant compared with the standard prophylactic dose. There was, however, no indication of increased bleeding with an intermediate dose compared with the standard prophylactic dose.

Treatment-dose anticoagulant

Two studies compared a treatment dose of an anticoagulant with the standard prophylactic dose (HESACOVID and ATTACC-ACTIV-4a-REMAP-CAP). The panel agreed that, for adults with severe COVID-19, the studies showed no statistically significant benefit for mortality or organ support-free days with a treatment dose of an anticoagulant compared with the standard prophylactic dose. There was no sign of increased bleeding with a treatment dose compared with the standard prophylactic dose.

Other considerations

The panel noted that 1 study showed an increase in ventilator-free days with treatment-dose anticoagulation. However, they agreed that the results were not certain enough to base a recommendation on because the study was very small.

The panel recommended not to base prophylactic dosing of heparin on levels of D-dimer because 1 trial presented evidence showing that a person's D-dimer measurements did not influence the effects of VTE prophylaxis.

Based on the lack of clear benefit with intermediate- or treatment-dose anticoagulation, the panel concluded that young people and adults with severe COVID-19 should be offered standard prophylactic-dose anticoagulation, and that intermediate- or treatment-dose VTE prophylaxis should not be used apart from as part of a clinical trial.

The panel discussed what to do if someone is already on treatment-dose anticoagulation at admission. They noted that people would normally remain on their prescribed anticoagulation if they can take oral medicines. However, they would switch to a low molecular weight heparin when they could no longer take oral medicines, such as when admitted to an intensive care unit.

Certainty of the Evidence

Low

INSPIRATION, REMAP-CAP, HESACOVID and Perepu et al. (2021) evaluated the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults having care for severe COVID-19.

The panel noted that the interventions that people had were mixed because of the local practices of the sites taking part in the trial. The panel recognised that the HESACOVID trial was very small and likely to be underpowered for the results it presented. Around 45% of people in INSPIRATION did not match the definition of 'severe COVID-19' used here. This was reflected in the lower rates of VTE than the committee expected to see in a population with severe COVID-19. The panel took these factors into account when considering the evidence.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences and values. The panel inferred that, in view of the lack of clear benefit of intermediate- or treatment-dose anticoagulation, most would choose a standard prophylactic dose of an anticoagulant.

Resources

No important issues with the recommended alternative

Cost effectiveness was not assessed as part of the evidence review.

The panel recommended that standard prophylactic-dose anticoagulation is used, rather than higher doses. This means there is expected to be no increase in cost related to the treatment.

Equity

No important issues with the recommended alternative

The panel noted an absence of evidence for anticoagulation in children. They recognised that younger children have different haematological physiology, meaning that VTE is less likely. However, their clinical experience suggested that, after puberty, people under 18 years are also at risk of VTE if admitted to hospital with COVID-19. For that reason, the panel included young people in the recommendations as well as adults. Additionally, a research recommendation was made for this population.

For people under 16 years, the risk of VTE is uncertain in the context of COVID-19. The risk benefit of VTE and dosing should preferably be discussed in multidisciplinary teams on a case-by-case basis considering all risk factors.

Not all heparins are acceptable to people of certain religions because the products are derived from animals. The panel made a recommendation about other treatments that can be used (including fondaparinux sodium, which is not animal derived).

No other equity issues were identified at this update.

Acceptability

No important issues with the recommended alternative

It is anticipated that, after considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with severe COVID-19 would choose to have standard prophylactic-dose anticoagulation. However, we have no systematically collected evidence about acceptability.

Feasibility

No important issues with the recommended alternative

Using standard prophylactic doses in young people and adults receiving high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation reflects usual treatment in some centres. For others, it is a minor treatment adjustment that should be feasible to implement.

Rationale

Based on the lack of clear benefit with intermediate- or treatment-dose anticoagulation, the panel concluded that young people and adults with severe COVID-19 should be offered standard prophylactic-dose anticoagulation. They also concluded that intermediate- or treatment-dose VTE prophylaxis should only be used as part of a clinical trial.

The panel were aware of ongoing trials of low molecular weight heparins (LMWHs) that use intermediate or treatment doses in this group of people, including REMAP-CAP. They agreed that intermediate- or treatment- dose LMWHs should only be used for VTE prophylaxis in this group as part of a clinical trial to support recruitment into these trials.

Clinical Question/ PICO

Population:	People with severe COVID-19
Intervention:	Treatment dose VTE prophylaxis
Comparator:	Standard dose VTE prophylaxis

Summary**What is the evidence informing this recommendation?**

Evidence comes from 2 randomised controlled trials with 1,089 participants included. Both studies (HESACOVID trial, reported in Lemos, 2020, n=20; and ACTIVE-41, ATACC, REMAP-CAP multiplatform trial, reported in Lawler, 2021, n=1,098) compared treatment dose anticoagulant (unfractionated heparin (UFH) or low molecular weight heparin (LMWH)) with either prophylactic or intermediate dose anticoagulant (mainly enoxaparin).

The comparator group varies between studies. In the HESACOVID trial, half of the comparator group received UFH and half received prophylactic dose enoxaparin. The ACTIVE-41, ATACC, REMAP-CAP trial combines data from three sites, each operating under their own protocols. The protocols are very similar but allow for local practice, meaning that just over 40% of the comparator arm received prophylactic dose enoxaparin, just over 50% received intermediate dose enoxaparin, and 7.4% received either subtherapeutic (dose unclear) or therapeutic dose of either UFH or LMWH. This may reduce the validity of the results from the ACTIVE-41, ATACC, REMAP-CAP trial.

Study characteristics

The mean age in the studies ranged from 55 to 61, and between 68% and 90% of participants were male. Both studies included only adult patients receiving intensive care unit-level respiratory or cardiovascular support. Data was collected from Australia, Brazil, Canada, Ireland, Mexico, Netherlands, New Zealand, Saudi Arabia, UK, and USA.

Exclusion criteria varied, but both studies excluded patients with a separate clinical indication for therapeutic anticoagulation. One study excluded patients over 85.

Duration of treatment was 4-14 days in HESACOVID, and up to 14 days or hospital discharge in ACTIVE-41, ATACC, REMAP-CAP.

What are the main results?**All-cause mortality**

Very low quality evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (LMWH or UFH) compared to either prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised. [Relative risk 0.33 CI 95% 0.04 - 2.69; 20 people in 1 study].

Death in hospital

Low quality evidence from a pooled analysis of 2 studies found no significant difference for death in hospital with treatment dose anticoagulant (LMWH at varying doses) compared with either UFH, enoxaparin or usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 1.03, CI 95% 0.89-1.21; 1,118 people in 2 studies].

Survival to hospital discharge

Low quality evidence from 1 study found no significant difference for survival to hospital discharge with treatment dose anticoagulant compared with usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 0.97, CI 95% 0.89-1.06; 1,098 people in 1 study].

Serious Adverse events: Major bleeding

Low quality evidence from a pooled analysis of 2 studies found no significant difference in major bleeding with treatment dose anticoagulant compared with prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised. [Relative risk 1.63, CI 95% 0.82 - 3.25; 1,111 people in 2 studies].

Organ-support free days at 21 days

Low quality evidence from 1 study found no statistically significant difference in organ-support free days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Odds Ratio 0.83, CI 95% 0.67 - 1.03; 1,098 people in 1 study].

Ventilator-free days

Low quality evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 15 versus 0; 20 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. The two studies were published manuscripts (ACTIVE-41, ATACC, REMAP-CAP and HESACOVID). Following the peer reviewed publication of ACTIVE-41, ATACC, REMAP-CAP (26/08/2021), the data for some of the outcomes was updated to reflect the latest figures in the published manuscript.

There were significant deviations from the intended interventions reported in one study (ACTIVE-41, ATACC, REMAP-CAP) whereby a large proportion of the comparator group received intermediate rather than prophylactic dose anticoagulant. In addition, almost 15% of the treatment group received either low or intermediate dose anticoagulant, where the intended intervention was treatment dose anticoagulant. This means the results from this study are unclear.

One study (HESACOVID) contained only 20 participants (10 in each arm). This trial did not have sufficient power to assess a difference in mortality, and results may be due to chance. This should be considered when looking at the increase in ventilator free days in the treatment group reported by this study.

Certainty of the evidence is very low for all-cause mortality due to serious risk of bias (deviation from intended control group treatment) and very serious imprecision (confidence intervals include the line of no effect and low numbers of participants).

Certainty of the evidence is low for death in hospital due to serious risk of bias, serious inconsistency (high statistical heterogeneity) and serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for survival to hospital discharge due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for major bleeding due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for organ support free days due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for ventilator-free days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals).

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality 28 days 9 Critical	Relative risk 0.33 (CI 95% 0.04 – 2.69) Based on data from 20 patients in 1 studies. ¹ (Randomized controlled)	300 per 1000 Difference:	99 per 1000 201 fewer per 1000 (CI 95% 288 fewer – 507 more)	Very low Due to serious risk of bias and very serious imprecision ²	Evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (unfractionated heparin or low molecular weight heparin) compared to either standard prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised.
Death in hospital 9 Critical	Relative risk 1.03 (CI 95% 0.89 – 1.21) Based on data from 1,118 patients in 2 studies. ³ (Randomized controlled)	357 per 1000 Difference:	368 per 1000 11 more per 1000 (CI 95% 39 fewer – 75 more)	Low Due to serious risk of bias, Due to serious imprecision ⁴	A pooled analysis of 2 studies found no statistically significant difference in death in hospital with treatment dose anticoagulant (low molecular weight heparin at varying doses) compared to either unfractionated heparin, enoxaparin or standard prophylactic dose anticoagulant

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Treatment dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
Survival to hospital discharge 9 Critical	Relative risk 0.97 (CI 95% 0.89 – 1.06) Based on data from 1,098 patients in 1 studies. ⁵ (Randomized controlled)	645 per 1000 Difference:	626 per 1000 19 fewer per 1000 (CI 95% 71 fewer – 39 more)	Low Due to serious risk of bias, Due to serious imprecision ⁶	(dose and treatment varies) for people who were hospitalised. Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.
Major bleeding 9 Critical	Relative risk 1.63 (CI 95% 0.82 – 3.25) Based on data from 1,111 patients in 2 studies. ⁷ (Randomized controlled)	23 per 1000 Difference:	37 per 1000 14 more per 1000 (CI 95% 4 fewer – 52 more)	Low Due to serious risk of bias, Due to serious imprecision ⁸	A pooled analysis of 2 studies found a non- statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.
Organ support free days 21 days 6 Important	Odds Ratio 0.83 (CI 95% 0.67 – 1.03) Based on data from 1,098 patients in 1 studies. (Randomized controlled)	567 per 1000 Difference:	536 per 1000 46 fewer per 1000 (CI 95% 100 fewer – 7 more)	Low Due to serious risk of bias, Due to serious imprecision ⁹	Evidence from 1 study found no statistically significant difference in organ support free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Ventilator-free days 28 days 6 Important	High better Based on data from: 20 patients in 1 studies. (Randomized controlled)	0 (Median)	15 (Median) CI 95%	Low Due to very serious imprecision ¹⁰	Evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

- Systematic review [78] with included studies: HESACOVID 2020, HESACOVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
- Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis, due to [reason]. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: very serious.** No statistically significant effect, and low number of patients., due to

[reason]. **Publication bias: no serious.**

3. Systematic review [93] with included studies: REMAP-CAP 2021, HESACOVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**

5. Systematic review [93] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**

7. Systematic review [93] with included studies: REMAP-CAP 2021, HESACOVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.

8. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**

9. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI includes line of no effect. **Publication bias: no serious.**

10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Unable to calculate effect size and 95% C.I.. **Publication bias: no serious.**

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Clinical Question/ PICO

Population: People with severe COVID-19
Intervention: Intermediate dose VTE prophylaxis
Comparator: Standard dose VTE prophylaxis

Summary

What is the evidence informing this recommendation?

Evidence comes from 2 randomised controlled trials with 735 participants included. Both studies (INSPIRATION trial, reported in Sadeghipour 2021 [for 30 day outcomes] and Bikdeli, 2021 [for 90 day outcomes], n=562 and Perepu 2021 n=173) compared intermediate dose enoxaparin (1mg/kg daily if the BMI was <30 or 0.5 mg/kg SC twice daily if the BMI was ≥30) with prophylactic dose enoxaparin (40mg daily).

The intervention and comparator groups were consistent between the studies. However, Perepu (2021) allowed for cointerventions, and more patients received azithromycin in the intermediate dose arm (29%) than in the prophylactic dose arm (13%).

Study characteristics

The mean age in the studies ranged from 61 to 65, and between 56% and 58% of participants were male. Both studies investigate the effects of the interventions in severe patients, but approximately 45% of the participants in the INSPIRATION trial were receiving low-flow oxygen and would therefore not be classed as having severe COVID-19 by the definitions used in the study protocol. The proportion of participants in Perepu (2021) receiving low-flow oxygen is unclear: it is reported that 62% were admitted to intensive care and 23% received invasive mechanical ventilation.

Data was collected from IRAN (INSPIRATION trial) and the USA (Perepu 2021).. Participants were excluded if they had recent known major bleeding or indications for a therapeutic dose of anticoagulant. Both studies excluded pregnant women. Duration of treatment was until hospital discharge (Perepu 2021) or for 30 and 90 days (INSPIRATION).

What are the main results?

All-cause mortality

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.01, CI 95% 0.84– 1.21; 735 people in 2 studies].

Low quality evidence from 1 study found no significant difference for all-cause mortality at 90 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.07, CI 95% 0.89 - 1.29; 562 people in 1 study]

Serious Adverse events: Major bleeding

Very low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with intermediate dose anticoagulant compared to prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised. [Relative risk 1.53, CI 95% 0.54 -4.28; 735 people in 2 studies]

Venous thromboembolism

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.02, CI 95% 0.52 – 2.00; 735 people in 2 studies]

Low quality evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 0.93, CI 95% 0.38 – 2.26; 562 people in 1 study]

Ventilator-free days

Very low quality evidence from 1 study found no significant difference for ventilator-free days at 30 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 30 days in intermediate dose group versus 30 days in prophylactic dose group; 562 people in 1 study].

Our confidence in the results

Both studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (Perepu, 21). The other study was from published manuscripts that reported 30 day and 90 day outcomes separately (INSPIRATION 2021).

Certainty of the evidence is low or very low for mortality outcomes due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for major bleeding due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for VTE outcomes at 30 days due to serious risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for VTE outcomes at 90 days to serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of evidence is very low for ventilator-free days at 30 days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals) and serious indirectness (dissimilarity between population of interest and those studied).

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Intermediate dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality 30 days 9 Critical	Relative risk 1.01 (CI 95% 0.84 – 1.21) Based on data from 735 patients in 2 studies. ¹ (Randomized controlled)	363 per 1000 Difference:	367 per 1000 4 more per 1000 (CI 95% 58 fewer – 76 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision ²	A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
All-cause mortality 90 days 9 Critical	Relative risk 1.07 (CI 95% 0.89 – 1.29) Based on data from 562 patients in 1 studies. ³ (Randomized controlled)	430 per 1000 Difference:	460 per 1000 30 more per 1000 (CI 95% 47 fewer – 125 more)	Low Due to serious indirectness and serious imprecision ⁴	Evidence from 1 study found no statistically significant difference in all-cause mortality at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

Outcome Timeframe	Study results and measurements	Comparator Standard dose VTE prophylaxis	Intervention Intermediate dose VTE prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain language summary
Major bleeding 9 Critical	Relative risk 1.53 (CI 95% 0.54 – 4.28) Based on data from 735 patients in 2 studies. ⁵ (Randomized controlled)	16 per 1000 Difference:	24 per 1000 8 more per 1000 (CI 95% 7 fewer – 52 more)	Very low Due to serious risk of bias, serious indirectness and serious imprecision ⁶	A pooled analysis of 2 studies found a non- statistically significant increase in major bleeding with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised.
VTE 30 days 9 Critical	Relative risk 1.02 (CI 95% 0.52 – 2) Based on data from 735 patients in 2 studies. ⁷ (Randomized controlled)	43 per 1000 Difference:	44 per 1000 1 more per 1000 (CI 95% 21 fewer – 43 more)	Very low Due to serious risk of bias, serious indirectness and serious imprecision ⁸	A pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
VTE 90 days 9 Critical	Relative risk 0.93 (CI 95% 0.38 – 2.26) Based on data from 562 patients in 1 studies. ⁹ (Randomized controlled)	35 per 1000 Difference:	33 per 1000 2 fewer per 1000 (CI 95% 22 fewer – 44 more)	Low Due to serious indirectness and serious imprecision ¹⁰	Evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Ventilator-free days 30 days 6 Important	High better Based on data from: 562 patients in 1 studies. (Randomized controlled)	30 (Median)	30 (Median) CI 95%	Very low Due to serious indirectness and very serious imprecision ¹¹	Evidence from 1 study found no statistically significant difference in ventilator-free days at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

1. Systematic review [83] with included studies: INSPIRATION 2021, Perepu 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious.** **Indirectness: serious.** Some patients have moderate in one study have moderate, not severe COVID-19. **Imprecision: serious.** No statistically significant effect. **Publication bias: no serious.**
3. Systematic review [79] with included studies: INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious.** **Indirectness: serious.** Differences between the population of interest and those studied.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**

5. Systematic review [79] with included studies: INSPIRATION 2021, Perepu 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients in one study have moderate, not severe COVID-19.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
7. Systematic review [79] with included studies: INSPIRATION 2021, Perepu 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients in one study have moderate, not severe COVID-19.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
9. Systematic review [79] with included studies: INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
11. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied.. **Imprecision: very serious.** Unable to calculate effect size and 95% C.I.. **Publication bias: no serious.**

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Consensus recommendation

Do not base prophylactic dosing of heparin on levels of D-dimer.

Evidence To Decision

Benefits and harms

See the evidence to decision sections for the [recommendation for treatment-dose VTE prophylaxis for young people and adults with COVID-19 who are receiving low-flow supplementary oxygen](#) and the [recommendation for treatment- and intermediate-dose VTE prophylaxis for young people and adults who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation](#).

Rationale

The panel agreed that D-dimer levels do not influence peoples' response to anticoagulation.

Consensus recommendation

For people at extremes of body weight or with impaired renal function, consider adjusting the dose of low molecular weight heparins in line with the summary of product characteristics and locally agreed protocols.

Rationale

This recommendation was adapted from the original NICE rapid guideline on reducing the risk of venous thromboembolism in over 16s with COVID-19 (now withdrawn) that considered intermediate doses in this population. In its development, the panel indicated that dose adjustments may be needed for people at extremes of body weight and those with renal impairment. To ensure that everyone gets an appropriate dose, the panel included dose adjustment in their recommendation. They added that summary of product characteristics and local protocols should be used to guide decisions on dose adjustment.

Consensus recommendation

For people who cannot have low molecular weight heparins (LMWHs), use fondaparinux sodium or unfractionated heparin (UFH).

In August 2021, LMWHs and fondaparinux sodium were off label for people under 18 years. See [NICE's information on prescribing medicines](#).

Consensus recommendation

For people who are already having anticoagulation treatment for another condition when admitted to hospital:

- continue their current treatment dose of anticoagulant unless contraindicated by a change in clinical circumstances
- consider switching to a low molecular weight heparin (LMWH) if their current anticoagulant is not an LMWH and their clinical condition is deteriorating.

Consensus recommendation

If a person's clinical condition changes, assess the risk of VTE, reassess bleeding risk and review VTE prophylaxis.

Consensus recommendation

Organisations should collect and regularly review information on bleeding and other adverse events in people with COVID-19 having treatment or intermediate doses of low molecular weight heparins.

Consensus recommendation

Ensure that people who will be completing VTE prophylaxis after discharge from hospital are able to use it correctly or have arrangements made for someone to help them.

8.3.1.1 In hospital-led acute care in the community

Consensus recommendation

For people with COVID-19 managed in hospital-led acute care in the community settings:

- assess the risks of VTE and bleeding
- consider pharmacological prophylaxis if the risk of VTE outweighs the risk of bleeding.

Rationale

There was no evidence to inform recommendations on reducing the risk of VTE in people with COVID-19 pneumonia managed in hospital-led acute care in the community settings with input from hospital clinicians, such as 'hospital at home' services or COVID-19 'virtual wards'. People whose condition is managed in these settings have an increased risk of VTE that is similar to that of people having management in hospital. The panel therefore included a recommendation to consider pharmacological VTE prophylaxis for these people to ensure that they have the same care as those admitted to hospital.

The panel also made a [recommendation for research on extending pharmacological VTE prophylaxis after discharge](#) in people who have had treatment for COVID-19 pneumonia.

8.3.2 People with COVID-19 and additional risk factors

Consensus recommendation

For women with COVID-19 who are pregnant or have given birth within the past 6 weeks, follow the [advice on VTE prevention in the Royal College of Obstetricians and Gynaecologists guidance on coronavirus \(COVID-19\) in pregnancy](#).

Rationale

The panel noted the lack of evidence on pharmacological VTE prophylaxis for people with COVID-19 and additional risk factors. They agreed that VTE risk in women with COVID-19 who are pregnant or have given birth in the past 6 weeks should be managed in line with advice on COVID-19 in pregnancy published by the Royal College of Obstetricians and Gynaecologists.

There was no evidence on pharmacological VTE prophylaxis for specific groups with additional risk factors for VTE, including people who are having treatment with sex hormones, have or have previously had cancer, are having renal replacement therapy or extracorporeal membrane oxygenation, have a clotting condition or history of VTE, or have obesity (body mass index 30 kg/m² or higher). The panel made a [recommendation for research on standard-dose compared with intermediate-dose pharmacological VTE prophylaxis](#) in people with COVID-19 who have additional risk factors for VTE.

Consensus recommendation

For children with COVID-19 admitted into hospital, follow the advice on [COVID-19 guidance for management of children admitted to hospital in the Royal College of Paediatrics and Child Health guidance](#).

8.3.3 Information and support

Consensus recommendation

Give people with COVID-19, and their families or carers if appropriate, information about the benefits and risks of VTE prophylaxis.

See the [recommendations on giving information and planning for discharge in the NICE guideline on venous thromboembolism in over 16s](#), including information on alternatives to heparin for people who have concerns about using animal products.

Consensus recommendation

Offer people the opportunity to take part in ongoing clinical trials on COVID-19.

8.4 Suspected or confirmed co-infection

Consensus recommendation

Do not offer an antibiotic for preventing or treating pneumonia if SARS-CoV-2, another virus, or a fungal infection is likely to be the cause.

*Antibiotics do not work on viruses, and inappropriate antibiotic use may reduce availability. Also, inappropriate use may lead to *Clostridioides difficile* infection and antimicrobial resistance, particularly with broad-spectrum antibiotics.*

Info Box

Evidence as of March 2021 suggests that bacterial co-infection occurs in less than about 8% of people with COVID-19, and could be as low as 0.1% in people in hospital with COVID-19. Viral and fungal co-infections occur at lower rates than bacterial co-infections.

Secondary infection or co-infection (bacterial, viral or fungal) is more likely the longer a person is in hospital and the more they are immunosuppressed (for example, because of certain types of treatment).

The type and number of secondary infections or co-infections will vary depending on the season and any restrictions in place (for example, lockdowns).

8.4.1 Identifying secondary bacterial pneumonia

Consensus recommendation

In hospitals or other acute delivery settings (for example, virtual wards), to help identify non-SARS-CoV-2 viral, fungal or bacterial pneumonia, and to inform decision making about using antibiotics, consider the following tests:

- a full blood count
- chest imaging (X-ray, CT or ultrasound)
- respiratory and blood samples (for example, sputum or a tracheal aspirate sample, blood culture; see [Public Health England's COVID-19: guidance for sampling and for diagnostic laboratories](#))
- urine samples for legionella and pneumococcal antigen testing
- throat samples for respiratory viral (and atypical pathogen) polymerase chain reaction testing.

Info Box

High C-reactive protein levels do not necessarily indicate whether pneumonia is due to bacteria or SARS-COV-2.

Low C-reactive protein level indicates that a secondary bacterial infection is less likely.

Consensus recommendation

Do not use C-reactive protein to assess whether a person has a secondary bacterial infection if they have been having immunosuppressant treatment.

Info Box

There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about antibiotics. Centres already using procalcitonin tests are encouraged to participate in research and data collection.

Procalcitonin tests could be useful in identifying whether there is a bacterial infection. However, it is not clear whether they add benefit beyond what is suggested in the [recommendation on tests to help differentiate between viral and bacterial pneumonia to guide decisions about antibiotics](#). The most appropriate threshold for procalcitonin is also uncertain.

8.4.2 Antibiotic treatment in the community

Consensus recommendation

Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.

Consensus recommendation

If a person has suspected or confirmed secondary bacterial pneumonia, start antibiotic treatment as soon as possible. Take into account any different methods needed to deliver medicines during the COVID-19 pandemic (see the [recommendation on minimising face-to-face contact in communication and shared decision making](#)).

Info Box

For antibiotic choices to treat community-acquired pneumonia caused by a secondary bacterial infection, see the recommendations on choice of antibiotic in the [NICE antimicrobial prescribing guideline on community-acquired pneumonia](#).

Consensus recommendation

Advise people to seek medical help without delay if their symptoms do not improve as expected, or worsen rapidly or significantly, whether they are taking an antibiotic or not.

Consensus recommendation

On reassessment, reconsider whether the person has signs and symptoms of more severe illness (see the [recommendation on signs and symptoms to help identify people with COVID-19 with the most severe illness](#)) and whether to refer them to hospital, other acute community support services or palliative care services.

8.4.3 Starting antibiotics in hospital

Consensus recommendation

Start empirical antibiotics if there is clinical suspicion of a secondary bacterial infection in people with COVID-19. When a decision to start antibiotics has been made:

- start empirical antibiotic treatment as soon as possible after establishing a diagnosis of secondary bacterial pneumonia, and certainly within 4 hours
- start treatment within 1 hour if the person has suspected sepsis and meets any of the high-risk criteria for this outlined in the [NICE guideline on sepsis](#).

8.4.4 Choice of antibiotics in hospital

Info Box

To guide decision making about antibiotics for secondary bacterial pneumonia in people with COVID-19, see the [NICE guideline on pneumonia \(hospital acquired\): antimicrobial prescribing](#).

Consensus recommendation

When choosing antibiotics, take account of:

- local antimicrobial resistance data and
- other factors such as their availability.

Consensus recommendation

Give oral antibiotics if the person can take oral medicines and their condition is not severe enough to need intravenous antibiotics.

Consensus recommendation

Consider seeking specialist advice on antibiotic treatment for people who:

- are immunocompromised
- have a history of infection with resistant organisms
- have a history of repeated infective exacerbations of lung disease
- are pregnant
- are receiving advanced respiratory support or organ support.

Consensus recommendation

Seek specialist advice if:

- there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic or
- there is clinical or microbiological evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.

8.4.5 Reviewing antibiotic treatment in hospital

Consensus recommendation

Review all antibiotics at 24 to 48 hours, or as soon as test results are available. If appropriate, switch to a narrower spectrum antibiotic, based on microbiological results.

For intravenous antibiotics, review within 48 hours and think about switching to oral antibiotics (in line with the [NICE guideline on pneumonia \(hospital-acquired\): antimicrobial prescribing](#))

Give antibiotics for 5 days, and then stop them unless there is a clear indication to continue (see the [recommendation on when to seek specialist advice](#)).

Consensus recommendation

Reassess people if their symptoms do not improve as expected, or worsen rapidly or significantly.

8.4.6 Ongoing review of co-infections in people with COVID-19

Info Box

We are currently reviewing new evidence on co-infections in people with COVID-19 as part of a living guidelines approach. New and updated recommendations will be published for this guideline as they become available (see [Update information | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE](#)).

9. Discharge, follow up and rehabilitation

Info Box

NICE is monitoring evidence on follow up, discharge and rehabilitation. Recommendations will be added in a future version of the guideline.

Info Box

For follow up and rehabilitation for people who have either ongoing symptomatic COVID-19 or post-COVID-19 syndrome, see the [NICE guideline on the long-term effects of COVID-19](#).

10. Palliative care

10.1 Principles of care

Info Box

For people who are nearing the end of their life, see:

- The [NICE guideline on care of dying adults in the last days of life](#): this includes recommendations on recognising when a person may be in the last days of life, communication and shared decision making.
- The [NICE guideline on end of life care for adults: service delivery](#): this includes recommendations for service providers on systems to help identify adults who may be at the end of their life, providing information and advanced care planning.
- The [NICE guideline on care and support of people growing older with learning disabilities](#): this includes recommendations on accessing end-of-life care services, person-centred care, and involving families and support networks in end-of-life care planning.

10.2 Medicines for end-of-life care

Consensus recommendation

Consider an opioid and benzodiazepine combination. See the table in practical info for managing breathlessness in the last days and hours of life for people 18 years and over with COVID-19 who:

- are at the end of life and
- have moderate to severe breathlessness and
- are distressed.

Consider concomitant use of an antiemetic and a regular stimulant laxative. Seek specialist advice for children and young people under 18 years.

Practical Info

Treatments in the last days and hours of life for managing breathlessness for people 18 years and over

Treatment	Dosage
	Higher doses may be needed for symptom relief in people with COVID-19. Lower doses may be needed because of the person's size or frailty
Opioid	The doses are based on the BNF and the Palliative care formulary Morphine sulfate 10 mg over 24 hours via a syringe driver, increasing stepwise to morphine sulfate 30 mg over 24 hours as required
Benzodiazepine if required in addition to opioid	Midazolam 10 mg over 24 hours via the syringe driver, increasing stepwise to midazolam 60 mg over 24 hours as required
Add parenteral morphine or midazolam if required	Morphine sulfate 2.5 mg to 5 mg subcutaneously as required Midazolam 2.5 mg subcutaneously as required (See the BNF for more details on dosages)
Special considerations	Consider concomitant use of an antiemetic and a regular stimulant laxative Continue with non-pharmacological strategies for managing breathlessness when starting an opioid Sedation and opioid use should not be withheld because of a fear of

Treatment	Dosage
	Higher doses may be needed for symptom relief in people with COVID-19. Lower doses may be needed because of the person's size or frailty
	The doses are based on the BNF and the Palliative care formulary causing respiratory depression

Info Box

For more recommendations on pharmacological interventions and anticipatory prescribing, see the [NICE guideline on care of dying adults in the last days of life](#) and prescribing information in the [BNF's prescribing in palliative care](#).

Consensus recommendation

For people with COVID-19 who are out of hospital, when prescribing and supplying anticipatory medicines at the end of life:

- Take into account potential waste, medicines shortages and lack of administration equipment by prescribing smaller quantities or by prescribing a different medicine, formulation or route of administration when appropriate.
- If there are fewer health and care staff, you may need to prescribe subcutaneous, rectal or long-acting formulations. Family members could be considered as an alternative option to administer medications if they so wish and have been provided with appropriate training.

Consensus recommendation

For people with COVID-19 who are out of hospital, consider different routes for administering medicines if the person is unable to take or tolerate oral medicines, such as sublingual or rectal routes, subcutaneous injections or continual subcutaneous infusions.

11. Research recommendations

What is the effectiveness and safety of standard-dose compared with intermediate-dose pharmacological venous thromboembolism (VTE) prophylaxis for people with COVID-19, with or without additional risk factors for VTE?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over being treated for COVID-19 pneumonia in hospital or the community who have:

- *no additional risk factors for VTE*
- *additional risk factors for VTE*

I: intermediate dose:

- *low molecular weight heparins (LMWH)*
- *unfractionated heparin (UFH)*
- *fondaparinux sodium*
- *direct-acting anticoagulant*
- *vitamin K antagonists*

C: Standard-dose:

- *LMWH*
- *UFH*
- *fondaparinux sodium*
- *direct-acting anticoagulants*
- *vitamin K antagonists*
- *antiplatelets*

O:

- *incidence of VTE*
- *mortality (all-cause, inpatient, COVID-19 related)*
- *admission to critical care (including use of advanced organ support)*
- *serious adverse events such as major bleeding or admission to hospital*

What is the effectiveness and safety of extended pharmacological venous thromboembolism (VTE) prophylaxis for people who have been discharged after treatment for COVID-19?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over who have been discharged after treatment for COVID-19 pneumonia

I: extended (2 to 6 weeks) pharmacological VTE prophylaxis with standard-dose:

- *low molecular weight heparins*
- *unfractionated heparins*
- *fondaparinux sodium*
- *direct-acting anticoagulant*
- *vitamin K antagonists*

C: No extended pharmacological VTE prophylaxis

O:

- *incidence of VTE*
- *mortality (all-cause, inpatient, COVID-19 related)*
- *serious adverse events such as major bleeding or admission to hospital*

What is the effectiveness and safety of a treatment dose with a low molecular weight heparin (LMWHs) compared with a standard prophylactic dose for venous thromboembolism (VTE) prophylaxis in young people under 18 years with COVID-19?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 18 years and under who have COVID-19 pneumonia

I: treatment-dose LMWH

C: standard prophylaxis with LMWH

O:

- *incidence of VTE*
- *mortality (all-cause, inpatient, COVID-19 related)*
- *admission to critical care (including use of advanced organ support)*
- *serious adverse events such as major bleeding or admission to hospital*

Does early review and referral to specialist palliative care services improve outcomes for adults with COVID-19 thought to be approaching the end of their life?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients with a confirmed diagnosis of COVID-19 in hospital or community approaching the last days of life

I: early referral to specialist palliative care services (for example, in the last days of life)

C: late referral (for example, within the final day of life) or no referral

O:

- *quality of life*
- *changes to clinical care*
- *patient or carer satisfaction (feeling supported)*
- *identification and/or achievement of patient wishes such as preferred place of death*

Is high-flow nasal oxygen effective in reducing breathlessness compared with standard care or conventional oxygen therapy for people in hospital with COVID-19 and respiratory failure when it is agreed that treatment will not be escalated beyond non-invasive respiratory support or palliative care is needed?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: adults over 18 years with COVID-19 having treatment for respiratory failure

I: high-flow nasal oxygen

C:

- *standard care*
- *conventional oxygen therapy*

O:

- *patient experience*
- *symptom improvement*
- *frequency of coughing*
- *assessment of breathing pattern disorder*
- *impact of breathlessness on activities of daily living such as eating, drinking and movement*
- *recovery of sense of smell*
- *practicalities of maintaining high-flow nasal oxygen at home for patients who wish their end of life care to occur at home.*

Subgroups: palliative care

Does a multidisciplinary team agreed approach to weaning from continuous positive airway pressure improve weaning times and result in stopping continuous positive airway pressure for people with COVID-19 and acute respiratory failure?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people with COVID-19 having continuous positive airway pressure for respiratory support

I: multidisciplinary team agreed approach to weaning

C:

- *standard care*
- *different multidisciplinary team approaches*

O:

- *patient experience*
- *symptom improvement*
- *length of time to wean*

Updated

What is the effectiveness, cost effectiveness and safety of using a combination of casirivimab and imdevimab at doses other than 8 g for treating COVID-19?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people hospitalised because of COVID-19

I: treatment with different doses of casirivimab and imdevimab

C:

- *recommended dose against different doses*
- *standard care against recommended dose and/or different doses*

O:

- *mortality*
- *progression to invasive mechanical ventilation*
- *progression to non-invasive respiratory support*
- *duration of hospitalisation*
- *adverse events*
- *costs of treatment*
- *health-related quality of life*

Updated

What is the effectiveness, cost effectiveness and safety of the combination of casirivimab and imdevimab for treating COVID-19 in people with particular clinical characteristics (for example, people who are seropositive, of unknown serostatus, immunocompromised, or with specific comorbidities and within both the seropositive and seronegative groups, according to vaccination status or history of natural infection)?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people hospitalised because of COVID-19

I: treatment with a combination of casirivimab and imdevimab

C:

- *treatment in people with different clinical characteristics (for example, people who are seropositive, of unknown serostatus, immunocompromised, or with specific comorbidities and within both the seropositive and seronegative groups, according to vaccination status or history of natural infection)*

O:

- *mortality*
- *progression to invasive mechanical ventilation*
- *progression to non-invasive respiratory support*
- *duration of hospitalisation*
- *adverse events*
- *costs of treatment*
- *health-related quality of life*

What is the clinical and cost effectiveness of budesonide for treating COVID-19 in the community in adults, young people and children?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: Adults, young people and children who have COVID-19 and are not in hospital

Subgroups of particular interest:

- *People 18 to 49 years*
- *Children and young people*

I: Inhaled budesonide

C: Inhaled placebo (to accommodate blinding)

O:

- *All-cause mortality*
- *Hospitalisation*
- *Need for oxygen therapy (including thresholds for this decision)*
- *Costs of treatment*
- *Time to recovery*
- *Health-related quality of life*
- *Adverse events*

12. Equality considerations

12.1 Equalities impact assessment during scoping - draft scope

Is the proposed primary focus of the guideline a population with a specific communication or engagement need, related to disability, age or other equality consideration?

No

Have any potential equality issues been identified during the check for an update or during development of the draft scope and, if so, what are they?

Exacerbating inequalities

There is potential for recommendations to exacerbate inequalities, if individual circumstances are not acknowledged. Protected characteristics and assumptions about individual circumstances need to be considered:

Sex

[Public Health England's report on disparities in the risk and outcomes of COVID-19](#) indicated that diagnosis rates of COVID-19 are higher in women under 40 years and men over 60 years. There are higher death rates from COVID-19 in men (nearly 60%) than women, and men make up a higher proportion of intensive care unit admissions (70% of admissions). This could mean that people in these groups may be at higher risk of poorer outcomes.

Age

[Public Health England's report on disparities in the risk and outcomes of COVID-19](#) highlighted that both diagnosis of COVID-19 and mortality are more likely as age increases (people 80 years or over are 70 times more likely to die than those under 40 years). Older people are more likely to be frail, and have comorbidities and underlying health conditions. These factors mean that people in these groups are at higher risk of poorer outcomes.

Older people may find it more difficult to access many services, including using digital technology to access remote consultations. This may increase the risk of them not being able to access appropriate services and care. Older people may need support from carers (both paid and unpaid) for both remote and face-to-face consultations, again this may increase the risk of them not being able to access the appropriate care. For some medications, different doses may be needed for older people. Whenever medication dosing is referred to, this should be used with information in the [BNF](#).

Ethnicity

[Public Health England's report on disparities in the risk and outcomes of COVID-19](#) identified that people from black, Asian and minority ethnic groups are at higher risk of getting COVID-19, more likely to have severe symptoms because of the infection and at higher risk of poorer outcomes. The highest age-standardised diagnosis rates of COVID-19 per 100,000 population are in people from black ethnic groups.

Survival analysis in people with confirmed COVID-19 (after accounting for sex, age, deprivation and region) indicated that people with a Bangladeshi family background have twice the risk of death compared with white British people. It also found that people with a Chinese, Indian, Pakistani, other Asian, Caribbean or other black family background had 10% to 50% higher risk of death compared with white British people. Emerging evidence suggests that excess mortality from COVID-19 is higher in black, Asian and minority ethnic groups. Individuals from black African or black Caribbean family backgrounds may have the highest risk.

Poorer outcomes in black, Asian and minority ethnic groups have been linked to several potential factors. These include higher rates of comorbidities that have been associated with COVID-19 mortality (such as cardiovascular disease, obesity and diabetes) in some black, Asian and minority ethnic populations. They also include a person's occupation (for example, over-representation in key worker roles in health and social care), and pre-existing socioeconomic factors such as housing conditions that could affect a person's ability to maintain infection control and prevention measures.

People from black, Asian and minority ethnic groups may feel marginalised, have experienced racism or have had previous experiences with a culturally insensitive health service that could create barriers to engagement with those services. This could mean that people in these groups may be at higher risk of poorer outcomes.

Disability

The scope of the guideline includes consideration of communication and shared decision making. For effective communication and shared decision making, specific consideration may need to be given to:

- people with a learning disability (including autism)
- people with a physical impairment (for example, a visual impairment or disability affecting communication)
- people with cognitive impairment (for example, mild or fluctuating dementia)
- people with a mental health issue.

The section on how to use this guideline states that it should be used alongside usual professional guidelines, standards and laws (including equalities, safeguarding, communication and mental capacity).

Socioeconomic factors

People who live in more socially deprived areas may be more likely to live in overcrowded housing and have occupations that might make them more at risk of being exposed to COVID-19.

Some people may not have access to the equipment needed to take part in digital consultations. Depending on where a person lives, they may not have access to home delivery services (for example, if they live in a rural area).

Gender reassignment

None identified.

Pregnancy and maternity

Not all medications are appropriate for people who are pregnant or breastfeeding. Whenever medication dosing is referred to, this should be used with information in the [BNF](#).

Religion or belief

Not all medications are acceptable to people of certain religions because of the products being animal derived. Whenever medication dosing is referred to, this should be used with information in the [BNF](#).

Sexual orientation

None identified.

Other definable characteristics

Examples are:

- refugees
- asylum seekers
- migrant workers
- people who are homeless.

For people whose first language is not English, there may be communication difficulties, especially for effective shared decision making and minimising risk of infection.

It is recognised that people who are homeless, refugees, asylum seekers and migrant workers may be living in deprived areas (including overcrowded accommodation), which may mean they are more likely to be exposed to COVID-19.

People from these groups may also be less likely to be able to access services.

What is the preliminary view on the extent to which these potential equality issues need addressing by the panel?

The guideline will need to address the potential equality issues by looking at data from studies either focused on the groups identified or looking at subgroup data. No groups will be excluded from the population.

The scope of this guideline does not include specific review of situations in which people lack mental capacity to make their own decisions about healthcare at that point in time. [NICE has produced guidance on decision making and mental capacity](#) to help health and social care practitioners:

- support people to make their own decisions as far as possible
- assess people's capacity to make specific health and social care decisions
- make specific best-interest decisions when people lack capacity, and maximise the person's involvement in those decisions.

12.2 Equalities impact assessment during scoping - final scope

Have any potential equality issues been identified during review of the draft scope, and, if so, what are they?

Yes. In addition to those outlined in section 12.1 on the equalities impact assessment on the draft scope, the following issues were identified. No changes were made to the scope on the basis of these issues.

Age

Some older people or people who are very frail may receive 'over-treatment' and this could remove them from familiar carers and surroundings.

Disability

A person's mental health can influence their health-seeking behaviours and how they manage their physical health conditions.

Gender reassignment

There may be an interplay between sex hormones in trans people. It is unknown whether sex differences in COVID-19 outcomes are due to genetics, hormonal issues or social factors.

Pregnancy and maternity

There has been an increased rate of maternal death since the start of the COVID-19 pandemic. It has also been reported that COVID-19 infection during pregnancy increases the risk of preterm birth, which is in turn linked to increased elective delivery and ventilation.

Race

There have been reports of vaccine hesitancy in people from black, Asian and minority ethnic groups. Given people in these groups are at risk of worse outcomes with COVID-19, vaccine hesitancy may further increase inequalities in outcomes.

Religion or belief

No further issues identified.

Sex

During the COVID-19 pandemic, women have had barriers to accessing in vitro fertilisation services, contraception and abortion care. Also, there have been increasing inequalities because of the lack of information being provided about alternative options.

Sexual orientation

Some people may feel marginalised because of their sexual orientation, so may have barriers to care because of their differing family or community structures.

Socio-economic factors

No further issues identified.

Were any changes to the scope made as a result of consultation to highlight potential equality issues?

No.

Have any of the changes made led to a change in the primary focus of the guideline which would require consideration of a specific communication or engagement need, related to disability, age, or other equality consideration?

If so, what is it and what action might be taken by NICE or the developer to meet this need? (For example, adjustments to panel processes, additional forms of consultation)

No. The equalities issues identified have not led to a change in the primary focus of the guideline.

12.3 Equalities impact assessment during guideline development

Have the potential equality issues identified during the scoping process been addressed by the panel, and, if so, how?

In the scoping process, a range of potential equality issues were identified. These have been addressed as follows:

Age

At scoping it was highlighted that older people with COVID-19 are at higher risk of poorer outcomes.

It was also noted that older people may have difficulties in accessing services, including using digital technology to access remote consultations, and that they may need carer support to access remote and face-to-face consultations. It is recommended in the [communication and shared decision making section](#) that, in the community, the risks and benefits of face-to-face and remote care should be considered for each person. This should allow issues such as an individual's ability to access remote care to be taken into account.

The panel also noted that some older people or people who are very frail could potentially receive 'over-treatment', which could remove them from familiar carers and surroundings. In the [section on care planning in the community](#), it is recommended to discuss with people with COVID-19, and their families and carers, the benefits and risks of hospital admission or other acute care delivery services (such as virtual wards, hospital at home teams). This should allow individualised decisions to be made that can take account of personal preferences to be cared for with familiar people in their usual surroundings.

It is noted that NEWS2 should not be used in children. This has been noted in the [section on identifying severe COVID-19 in the community](#). The panel recommended the use of locally approved paediatric early warning scores in children.

Sex

It has been reported that there are higher death rates from COVID-19 in men than women and that men comprise a higher proportion of intensive care unit admissions. While this guideline does not make specific recommendations based on sex, the guideline allows for consideration of individual characteristics and risk factors in planning care. For example, in the [section on assessment in hospital the guideline](#) recommends that, on admission to hospital, a holistic assessment should be completed.

It was also noted that, during the COVID-19 pandemic, women have experienced barriers to accessing in vitro fertilisation services, contraception and abortion care. The provision of these services are outside the scope of this guideline.

Gender reassignment

It was noted during scoping that there may be an interplay between sex hormones in trans people and it is not known if sex differences in COVID-19 outcomes are due to genetic, hormonal or social factors. The panel did not make specific recommendations based on gender reassignment.

Sexual orientation

Some people may feel marginalised due to their sexual orientation and therefore may have barriers to care due to their differing family or community structures. No recommendations were made specific to sexual orientation.

Ethnicity

Emerging evidence suggests that excess mortality due to COVID-19 is higher in black, Asian and minority ethnic groups. The guideline does not make specific recommendations according to ethnicity. However, alongside the [recommendation relating to the use of pulse oximetry](#) it is noted that overestimation has been reported in people with dark skin.

There have been reports of vaccine hesitancy in people of from black, Asian and minority ethnic groups. Given that these groups are at risk of worse outcomes with COVID-19, vaccine hesitancy may further increase inequalities in outcomes. Vaccine uptake is outside the scope of this guideline.

Disability

Regarding communication and shared decision making, specific consideration may need to be given to people with a learning disability, people with physical impairments, people with cognitive impairment, and people with mental health issues. The [section on communication and shared decision making](#) recommends communicating with people with COVID-19, their families and carers to alleviate any fear or anxiety. This recommendation also advises to provide people with information in a way that they can use and understand, and to follow national guidance on communication, providing information (including in different formats and languages) and shared decision making. The guideline also recommends involving families and carers where appropriate to support discussions relating to care and shared decision making.

We state that this guideline should be used alongside usual professional guidelines, standards and laws (including equalities, safeguarding, communication and mental capacity).

It has also been noted that a person's mental health can influence their health-seeking behaviours and how they manage their physical health conditions. As above, the guideline recommends involving families and carers in discussions relating to care where appropriate.

Socioeconomic factors

People who live in more socially deprived areas may be more likely to live in conditions and have occupations that may increase the risk of being exposed to COVID-19. No recommendations were made based on levels of social deprivation, living conditions or occupation.

Some people may not have access to equipment needed for remote consultations. It is recommended in the [section on communication and shared decision making](#) that, in the community, the risks and benefits of face-to-face and remote care should be considered for each person. This should allow issues such as an individual's ability to access remote care to be considered.

Depending on where a person lives (for example in rural areas), they may have difficulty accessing home delivery services. The guideline recommends optimising remote care where appropriate, such as pharmacy deliveries, postal services, NHS volunteers and introducing drive-through pick up points for medicines. Providing a range of potential options may support access in different geographical areas. The guideline also covers use of anticipatory medicines at end of life. It is noted that, if there are fewer health and care staff, differing formulations may be prescribed and family members may be able to support administration of medications if they wish and have been provided with appropriate training.

Pregnancy and maternity

At scoping, increased rates of maternal death and an increased risk of preterm birth during the COVID-19 pandemic were highlighted. No recommendations were made specifically on pregnancy.

It is noted that NEWS2 should not be used when pregnant. This has been noted in the [relevant recommendation under identifying severe COVID-19](#).

As not all medications are appropriate for people who are pregnant or breastfeeding, whenever medication dosing is referred to, this should be used with information in the [BNF](#).

Religion or belief

Not all medications are acceptable to people of certain religions due to the products being animal derived.

Other definable characteristics

For people whose first language is not English, there may be communication difficulties, especially relating to shared decision making and minimising risk of infection. The [section on communication and shared decision making](#) recommends communicating with people with COVID-19, their families and carers to alleviate any fear or anxiety. This recommendation also advises to provide people with information in a way that they can use and understand, and to follow national guidance on communication, providing information (including in different formats and languages) and shared decision making.

People who are homeless, refugees, asylum seekers and migrant workers may be living in deprived areas (including overcrowded accommodation) and so may be more likely to be exposed to COVID-19 and may also experience difficulties in accessing services. No recommendations were made specific to people who are homeless, refugees, asylum seekers and migrant workers.

Have any other potential equality issues (in addition to those identified during the scoping process) been identified, and, if so, how has the panel addressed them?

Disability

The panel identified that children and young people under 18 years, or people with learning disabilities, may need additional consideration around capacity and decision making because of the isolated nature of treatment. The panel agreed that a recommendation should be added stating that, when making decisions about care of children and young people under 18 years, people with learning disabilities or adults who lack mental capacity for health decision making, the [NICE guideline on decision making and mental capacity](#) should be referred to. It was also recommended to ensure that discussions on significant care interventions involve family and carers, as appropriate, and local experts or advocates. The panel noted that infection prevention and control, including self-isolation, may be more challenging for some groups of people, including those with dementia or learning disabilities. A recommendation has been added to advise that, for carers of people with COVID-19 who should isolate but are unable to, relevant support and resources should be signposted to (for example, Alzheimer's society has information on staying safe from coronavirus and reducing the risk of infection).

Ethnicity

It was noted that pulse oximeters can be less accurate in people with dark skin, especially at the borderline range of 90% to 92%. Information about this has been added to the recommendation to alert healthcare practitioners to this.

Religion or belief

The panel identified that, for people who do not use animal products, honey would not be appropriate for cough. No change was made to this recommendation.

Do the preliminary recommendations make it more difficult in practice for a specific group to access services compared with other groups? If so, what are the barriers to, or difficulties with, access for the specific group?

No. None identified.

Is there potential for the preliminary recommendations to have an adverse impact on people with disabilities because of something that is a consequence of the disability?

No.

Are there any recommendations or explanations that the panel could make to remove or alleviate barriers to, or difficulties with, access to services identified, or otherwise fulfil NICE's obligation to advance equality?

Not applicable.

13. Methods and processes

Development

This guideline was developed using the methods and process in our [interim process and methods for guidelines developed in response to health and social care emergencies](#).

Structure

The guideline structure follows the main themes and overarching questions set out in the scope. Existing NICE COVID-19 rapid guidelines and international guidelines were reviewed to inform further subsections. The structure was designed to allow flexibility to refine, remove or add sections in future iterations within a living approach. The guideline includes disease severity definitions that are in line with WHO definitions and approved by the NICE expert advisory panel. These are used to inform severity-specific recommendations where applicable.

Mapping of existing content

We compiled a list of all recommendations in the COVID-19 rapid guidelines that were relevant to the scope of this guideline. These recommendations were added to the appropriate section in the draft structure of the new guideline. After NICE technical and clinical quality assurance of this mapping work, the recommendations were transferred to the relevant part of the structure on the publishing platform MAGICapp.

After the initial mapping, the structure was refined. The NICE expert advisory panel identified gaps in coverage and any recommendations that should be changed. The panel were also asked whether any of the recommendations from the rapid guidelines could be removed, if no longer relevant, due to new emergent evidence or due to recommendations being context specific and therefore bound to a particular time in the pandemic. Any changes to recommendation content were based on the consensus view of the expert advisory panel.

Therapeutics for COVID-19

Reviewing the evidence

As there is a need for prompt guidance on therapeutics for managing COVID-19, NICE is collaborating with other guideline development teams to produce evidence reviews. NICE has reused data from the [National Australian COVID-19 clinical evidence taskforce](#) for some recommendations. As the time of publication (March 2021), no specific literature searches were carried out for the therapeutics section of the guideline.

The use of evidence provided by the National Australian COVID-19 clinical evidence taskforce is achieved through the sharing of RevMan files, which the NICE team use to populate the evidence summary section and GRADE profiles for a review.

Because therapeutics for managing COVID-19 is an emerging area, data provided by other guideline developers may be supplemented with additional trial results that the NICE COVID-19 team have access to. Relevant trials are identified through NICE's [Rapid C-19 initiative](#). On occasion, NICE may be given access to trial data before publication in a peer review journal (academic in confidence data). Data extraction and risk of bias will be carried out in line with the [interim process and methods for guidelines developed in response to health and social care emergencies](#). Where academic-in-confidence data is used, this will be described in the evidence to decisions summary for that section of the guideline. As this is a living guideline, trial results from academic in confidence data will be revisited when published and reconsidered by the expert advisory panel.

All evidence reviews are quality assured before they are presented to the expert advisory panel. For reviews generated by the National Australian COVID-19 clinical evidence taskforce, the expert advisory panel will assess the relevance and applicability to the UK context, which will feed into the considerations for developing the recommendations.

Expert advisory panel members and declarations of interest

Declarations of interest (DOI) were recorded according to the [2019 NICE conflicts of interest policy](#). For a list of panel members and corresponding DOI registry for this guideline see the [NICE guideline page on managing COVID-19](#).

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