# COVID-19 rapid guideline: Managing COVID-19

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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:
This recommendation is informed by the results of the RECOVERY trial, which recruited people between 18 September 2020 and 22 May 2021. This was before the emergence of the Omicron (B.1.1.529) variant. In vitro data suggests that the efficacy of casirivimab and imdevimab is likely to be compromised against this variant. NICE will review and update this recommendation as further evidence emerges.

The criteria for accessing neutralising monoclonal antibodies (nMABS) for people hospitalised 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 December 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given neutralising monoclonal antibodies.

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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.

Remark:
This recommendation is informed by the results of the RECOVERY trial, which recruited people between 18 September 2020 and 22 May 2021. This was before the emergence of the Omicron (B.1.1.529) variant. In vitro data suggests that the efficacy of casirivimab and imdevimab is likely to be compromised against this variant. NICE will review and update this recommendation as further evidence emerges.

The criteria for accessing neutralising monoclonal antibodies (nMABS) for people hospitalised 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 December 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given neutralising monoclonal antibodies.

## 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

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

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

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 Updated

Do not use colchicine to treat COVID-19.

## 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 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.

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.

## 9. Identifying and managing co-infections

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).

## 9.1 Bacterial pneumonia

### 9.1.1 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.

### 9.1.2 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.

### 9.1.3 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.

### 9.1.4 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.

### 9.1.5 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.

## 9.2 COVID-19-associated pulmonary aspergillosis (CAPA)

Info Box New

For people who are critically ill and have, or have had, COVID-19 as part of their acute illness:

- CAPA is a recognised cause of someone's condition not improving despite treatment (for example, antibiotic therapy, ventilatory support)
- there are no specific combinations of signs or symptoms for diagnosing CAPA
- the risk of having CAPA may increase with age and chronic lung disease.

### 9.2.1 Diagnosing CAPA

Consensus recommendation New

When deciding whether to suspect CAPA in someone who is critically ill and has, or has had, COVID-19 as part of their acute illness:

- base your decisions on individual risk factors and the person's clinical condition
- involve a multidisciplinary team, including infection specialists
- refer to local protocols on diagnosing and managing CAPA.

Remark:
Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.

Not recommended New

Do not do diagnostic tests for CAPA if there is low clinical suspicion of the condition.

Recommended New

When investigating suspected CAPA:

- use a range of tests to increase the likelihood of making a confident diagnosis
- if possible, include bronchoalveolar lavage (BAL) as part of diagnostic testing, taking into account the risks of BAL in relation to the person's clinical condition
- discuss the diagnostic testing strategy and final diagnosis with a multidisciplinary team that includes infection specialists.

Consensus recommendation New

Test for antifungal resistance if an Aspergillus isolate is cultured from a CAPA test sample.

Consensus recommendation New

Commissioners and local trusts should ensure that results of diagnostic tests for CAPA are available in a timeframe that informs and supports clinical decision making.

Consensus recommendation New

Monitor and report testing for, and diagnosis and management of, CAPA in line with local protocols.

Remark:
Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.

### 9.2.2 Treating CAPA

Consensus recommendation New

Only use antifungal treatments to treat CAPA if:

- diagnostic investigations support a diagnosis of CAPA or
- the results of diagnostic investigations are not available yet, but CAPA is suspected, and a multidisciplinary team or local protocols support starting treatment.

Remark:
See NICE's recommendations on diagnosing CAPA.

Recommended New

When considering antifungal treatment for CAPA:

- discuss treatment options with a multidisciplinary team that includes infection specialists
- follow local protocols that include best practice guidance on treating invasive aspergillosis.

Remark:
There is not enough evidence to recommend specific antifungal treatments for CAPA.

The panel noted the importance of national antifungal stewardship guidance, such as NICE's guideline on antimicrobial stewardship.

Consensus recommendation New

For people having antifungal treatment for suspected CAPA, stop treatment if the results of investigations do not support a diagnosis of CAPA and a multidisciplinary team agrees.

## 10. 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.

## 11. Palliative care

### 11.1 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.

### 11.2 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.

## 12. 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

### 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

### 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

### 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

New

### What risk factors in people who are critically ill and have, or have had, COVID-19 as part of their acute illness are associated with developing COVID-19-associated pulmonary aspergillosis (CAPA)?

Remark:
Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness. Subgroups of particular interest include children and young people, and pregnant women.

Exposure: any

Outcomes:

- association of CAPA with individual factors (for example, age, sex, ethnicity, comorbidities, COVID-19 vaccination status,)
- association of CAPA with COVID-19 treatments (for example, respiratory support for COVID-19, high-dose corticosteroids, interleukin-6 inhibition)
- association of CAPA with length of stay in hospital

New

### What are the possible outcomes for people who are critically ill and have COVID-19-associated pulmonary aspergillosis (CAPA)?

Remark:
Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and who have CAPA. Subgroups of particular interest: young people and children, pregnant women, ethnicity, immunosuppression and subgroups who have higher rates of COVID-19

Outcomes:

- presence of fungal serum biomarkers (for example galactomannan and beta-D-glucan)
- measures of inflammation (for example C-reactive protein)
- need for respiratory support (for example, invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO])
- hospitalisation metrics (for example, mortality, length of hospital stay, admission to and length of stay in intensive care)
- long-term morbidity outcomes, functional measures and patient outcomes
- results may be stratified (for example, disease severity, use of ECMO)

New

### In people with suspected COVID-19-associated pulmonary aspergillosis (CAPA), what are the most accurate tests for diagnosing the infection and when should they be done?

Remark:
Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and suspected CAPA. Subgroups of particular interest include young people and children, and pregnant women.

Diagnostic tests:

- any methods used to diagnose pulmonary aspergillosis (for example, CT imaging, testing of bronchoalveolar lavage, non-bronchoscopic lavage, endotracheal aspirate, sputum samples, serum assays)

Reference standard:

- lung biopsy or postmortem diagnosis

Target condition:

- CAPA

Outcomes:

- sensitivity and specificity
- positive and negative likelihood ratios

Analysis:

- optimal time of diagnostic testing

New

What are the views, preferences and experiences of people with COVID-19-associated pulmonary aspergillosis (CAPA), and their families or carers, on:

- available tests for diagnosing CAPA
- available treatments for CAPA?

Remark:
Suggested PIC (Population, Interest, Context)

P: people who have been diagnosed with and treated for CAPA, and their families or carers. Subgroups of particular interest include young people and children, and pregnant women.

I: tests for diagnosing CAPA and treatments for CAPA

C: people who have been diagnosed with, and had treatment for, CAPA in hospital

New

What are the clinical and cost effectiveness, and the safety, of specific antifungal treatments for treating suspected or confirmed COVID-19-associated pulmonary aspergillosis (CAPA), and the optimal treatment duration? When should treatment be started, stopped or modified?

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

P: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness and have probable or diagnosed CAPA. Subgroups of particular interest: children and young people, pregnant women, ethnicity, immunosuppression, and subgroups who have higher rates of COVID-19.

I: voriconazole, isavuconazole, liposomal amphotericin B, posaconazole, echinocandins (for example, caspofungin, anidulafungin) and amphotericin B deoxycholate

C: Standard care (usually voriconazole)

O:

- all-cause mortality (at any time during treatment)
- number of people having 1 or more serious adverse events
- number of days without respiratory or organ support (organ support includes use of vasopressors and renal replacement therapy)
- length of stay in intensive care
- number of people having 1 or more adverse events
- treatment duration
- timing of starting treatment
- need for treatment modification
- length of hospital stays
- need for and duration of invasive mechanical ventilation
- need for switching, starting or restarting antifungal treatment

## 13. Equality considerations

### 13.1 Equalities impact assessment during scoping - draft scope

### 13.2 Equalities impact assessment during scoping - final scope

### 13.3 Equalities impact assessment during guideline development

## 14. 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<br>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<br>Increase up to 5 mg to 10 mg every 4 hours as required<br>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 |
|---|---|
| | 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<br><br>The doses are based on the BNF and the Palliative care formulary |
| **Anxiety or agitation and able to swallow**: lorazepam tablets | Lorazepam 0.5 mg to 1 mg four times a day as required (maximum 4 mg in 24 hours)<br>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)<br>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<br>If needed frequently (more than twice daily), a subcutaneous infusion via a syringe |

| Treatment | Dosage |
|---|---|
| | driver may be considered (if available) starting with midazolam 10 mg over 24 hours<br>Reduce dosage to 5 mg over 24 hours if estimated glomerular filtration rate is less than 30 ml per minute |
| **Delirium and able to swallow:** haloperidol tablets | 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)<br>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<br>Consider a higher starting dose (1.5 mg to 3 mg) if the person is severely distressed or causing immediate danger to others<br>Consider adding a benzodiazepine such as lorazepam or midazolam if the person remains agitated (see dosages above) |
| **Delirium and unable to swallow**: levomepromazine injection | 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)<br>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)<br>Consider midazolam alone or in combination with levomepromazine if the person also has anxiety (see dosages above)<br>**Special considerations**<br>Seek specialist advice for people under 18 years old |

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 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 (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) | 17.3 days (Mean) Difference: | 16.4 days (Mean) **MD 0.97 fewer** ( CI 95% 3.65 fewer — 1.71 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 CPAP compared with conventional oxygen in people with COVID-19. |
| 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 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 (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) | 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. |

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 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 (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** ( 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 ) | 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 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 (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) | 17.3 days (Mean) Difference: | 16.4 days (Mean) **MD 0.97 fewer** ( CI 95% 3.65 fewer — 1.71 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 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** |
|---|---|---|---|---|---|
| Mean length of stay in critical care (days) | Lower better (Randomized controlled) | 9.6 (Mean)<br><br>Difference: | 9.5 (Mean)<br><br>**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 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 (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. |

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 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 (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, $PaO_2/FiO_2 < 200$, positive end-expiratory pressure (PEEP) ≥ 5 cm $H_2O$, 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<br>9 Critical | 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<br>Difference: | 178 per 1000<br>**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. |
| Invasive mechanical ventilation or death [adults requiring oxygen] [4] Within 28 days of commencing treatment<br>9 Critical | 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<br>Difference: | 282 per 1000<br>**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. |
| Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days of commencing treatment<br>9 Critical | 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<br>Difference: | 194 per 1000<br>**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. |
| Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment<br>9 Critical | 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<br>Difference: | 772 per 1000<br>**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. |
| 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<br>Difference: | 640 per 1000<br>**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<br><br>9 Critical | controlled) | | ( CI 95% 35 more — 87 more ) | | compared with standard care in adults who require oxygen. |
| **Serious adverse events [adults requiring oxygen]**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.8<br>(CI 95% 0.53 — 1.19)<br>Based on data from 696 patients in 6 studies. [12]<br>(Randomized controlled) | 234<br>per 1000<br><br>Difference: | 187<br>per 1000<br><br>**47 fewer per 1000**<br>( CI 95% 110 fewer — 44 more ) | **Moderate**<br>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**<br>End of treatment<br><br>6 Important | Relative risk 1.06<br>(CI 95% 0.82 — 1.33)<br>Based on data from 5,403 patients in 30 studies. | 48<br>per 1000<br><br>Difference: | 51<br>per 1000<br><br>**3 more per 1000**<br>( CI 95% 9 fewer — 16 more ) | **Low**<br>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**<br>End of treatment<br><br>6 Important | Relative risk 1.01<br>(CI 95% 0.9 — 1.13)<br>Based on data from 6,027 patients in 32 studies. | 186<br>per 1000<br><br>Difference: | 188<br>per 1000<br><br>**2 more per 1000**<br>( CI 95% 19 fewer — 24 more ) | **Low**<br>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**<br>End of treatment<br><br>6 Important | Relative risk 1.16<br>(CI 95% 1.08 — 1.25)<br>Based on data from 8,938 patients in 24 studies. | 286<br>per 1000<br><br>Difference: | 332<br>per 1000<br><br>**46 more per 1000**<br>( CI 95% 23 more — 72 more ) | **Moderate**<br>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**<br>End of treatment<br><br>6 Important | Relative risk 1.09<br>(CI 95% 0.86 — 1.39)<br>Based on data from 6,358 patients in 8 studies. | 69<br>per 1000<br><br>Difference: | 75<br>per 1000<br><br>**6 more per 1000**<br>( CI 95% 10 fewer — 27 more ) | **Low**<br>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. |
| **Neuropsychiatric effects**<br>End of treatment | Relative risk 0.81<br>(CI 95% 0.41 — 1.63)<br>Based on data from 1,813 patients in 7 studies. | 35<br>per 1000<br><br>Difference: | 28<br>per 1000<br><br>**7 fewer per 1000**<br>( CI 95% 21 fewer | **Low**<br>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: CAPE COVID 2020, METCOVID 2020, Steroids-SARI 2020, COVID STEROID 2020, RECOVERY, DEXA-COVID 19 2020, REMAP-CAP 2020, CoDEX 2020, RECOVERY, Edalatifard 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, Edalatifard 2020, RECOVERY. **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: REMAP-CAP 2020, Steroids-SARI 2020, DEXA-COVID 19 2020, CoDEX 2020, CAPE COVID 2020, COVID STEROID 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).

*This recommendation is informed by the results of the RECOVERY trial, which recruited people between 18 September 2020 and 22 May 2021. This was before the emergence of the Omicron (B.1.1.529) variant. In vitro data suggests that the efficacy of casirivimab and imdevimab is likely to be compromised against this variant. NICE will review and update this recommendation as further evidence emerges.*

*The criteria for accessing neutralising monoclonal antibodies (nMABS) for people hospitalised 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 December 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given neutralising monoclonal antibodies.*

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## 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 December 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 16 December 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 $m^2$). 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 | Relative risk 0.94 (CI 95% 0.87 — 1.02) Based on data from 9,785 patients in 1 | 207 per 1000 | 195 per 1000 | **Moderate** Due to serious imprecision [2] | One study found no statistically significant difference in mortality for all participants |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Usual Care | **Intervention** Casirivimab + Imdevimab | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| 9 Critical | studies. [1] (Randomized controlled) | Difference: | **12 fewer per 1000** ( CI 95% 27 fewer — 4 more ) | | 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<br>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<br>Difference: | 155 per 1000<br>**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<br>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<br>Difference: | 244 per 1000<br>**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<br>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<br>Difference: | 105 per 1000<br>**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<br>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<br>Difference: | 185 per 1000<br>**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 | Odds Ratio 0.76 (CI 95% 0.66 — 0.88) Based on data from | 365 per 1000 | 304 per 1000 | High | One study found a statistically significant reduction in progression |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Usual Care | **Intervention** Casirivimab + Imdevimab | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| [Seronegative] Within 28 days of randomisation<br>9 Critical | 3,083 patients in 1 studies. [9] (Randomized controlled) | Difference: | **61 fewer per 1000** ( CI 95% 90 fewer — 29 fewer ) | | 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<br>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<br>Difference: | 219 per 1000<br>**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<br>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<br>Difference: | 268 per 1000<br>**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<br>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<br>Difference: | 4 per 1000<br>**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<br>6 Important | Lower better Based on data from: 9,785 patients in 1 studies. (Randomized controlled) | 10 (Median) | 10 (Median)<br>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 | Lower better Based on data from: 3,153 patients in 1 studies. (Randomized controlled) | 17 (Median) | 13 (Median)<br>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 |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Usual Care | **Intervention** Casirivimab + Imdevimab | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| 6 Important | | | | | 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.

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.

*This recommendation is informed by the results of the RECOVERY trial, which recruited people between 18 September 2020 and 22 May 2021. This was before the emergence of the Omicron (B.1.1.529) variant. In vitro data suggests that the efficacy of casirivimab and imdevimab is likely to be compromised against this variant. NICE will review and update this recommendation as further evidence emerges.*

*The criteria for accessing neutralising monoclonal antibodies (nMABS) for people hospitalised 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 December 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given neutralising monoclonal antibodies.*

## 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 December 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 16 December2021, 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 $m^2$). 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<br><br>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<br><br>Difference: | 195 per 1000<br><br>**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] | Relative risk 1.07 (CI 95% 0.94 — 1.22) | 145 | 155 | Moderate Due to serious | One study found no statistically significant |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Usual Care | **Intervention** Casirivimab + Imdevimab | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| Within 28 days of randomisation<br><br>9 Critical | Based on data from 5,272 patients in 1 studies. [3] (Randomized controlled) | per 1000<br><br>Difference: | per 1000<br><br>**10 more per 1000**<br>( CI 95% 9 fewer — 32 more ) | imprecision [4] | 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]<br>Within 28 days of randomisation<br><br>9 Critical | Relative risk 0.82<br>(CI 95% 0.73 — 0.92)<br>Based on data from 3,153 patients in 1 studies. [5] (Randomized controlled) | 297<br>per 1000<br><br>Difference: | 244<br>per 1000<br><br>**53 fewer per 1000**<br>( 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]<br>Within 28 days of randomisation<br><br>9 Critical | Relative risk 1<br>(CI 95% 0.89 — 1.13)<br>Based on data from 9,198 patients in 1 studies. [6] (Randomized controlled) | 105<br>per 1000<br><br>Difference: | 105<br>per 1000<br><br>**0 fewer per 1000**<br>( CI 95% 12 fewer — 14 more ) | Moderate<br>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]<br>Within 28 days of randomisation<br><br>9 Critical | Odds Ratio 1.17<br>(CI 95% 1.01 — 1.36)<br>Based on data from 4,989 patients in 1 studies. [8] (Randomized controlled) | 163<br>per 1000<br><br>Difference: | 185<br>per 1000<br><br>**23 more per 1000**<br>( 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]<br>Within 28 days of randomisation<br><br>9 Critical | Odds Ratio 0.76<br>(CI 95% 0.66 — 0.88)<br>Based on data from 3,083 patients in 1 studies. [9] (Randomized controlled) | 365<br>per 1000<br><br>Difference: | 304<br>per 1000<br><br>**61 fewer per 1000**<br>( 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 | Odds Ratio 0.94 | 230 | 219 | High | One study found no |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Usual Care | **Intervention** Casirivimab + Imdevimab | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| ventilation [All patients] Within 28 days of randomisation<br><br>6 Important | (CI 95% 0.84 — 1.05) Based on data from 6,637 patients in 1 studies. [10] (Randomized controlled) | per 1000<br><br>Difference: | per 1000<br><br>**11 fewer per 1000** ( CI 95% 29 fewer — 9 more ) | | 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<br><br>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<br><br>Difference: | 268 per 1000<br><br>**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<br><br>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<br><br>Difference: | 4 per 1000<br><br>**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<br><br>6 Important | Lower better Based on data from: 9,785 patients in 1 studies. (Randomized controlled) | 10 (Median) | 10 (Median)<br><br>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<br><br>6 Important | Lower better Based on data from: 3,153 patients in 1 studies. (Randomized controlled) | 17 (Median) | 13 (Median)<br><br>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 | Biegel 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 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<br><br>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<br><br>Difference: | 65 per 1000<br><br>**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 |

| **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 (High flow oxygen, NIV or IMV) [4] Within 28 days of commencing treatment<br>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<br>Difference: | 298 per 1000<br>**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<br>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<br>Difference: | 128 per 1000<br>**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<br>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<br>Difference: | 190 per 1000<br>**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<br>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<br>Difference: | 113 per 1000<br>**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<br>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<br>Difference: | 118 per 1000<br>**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<br>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<br>Difference: | 10 per 1000<br>**0 fewer per 1000** ( CI 95% 7 fewer — 20 more ) | Very low Due to serious risk of bias, serious inconsistency and serious | Two studies found no statistically significant difference in septic shock 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** |
|---|---|---|---|---|---|
| | | | | imprecision [18] | |
| **Clinical recovery**<br>Within 28 days of commencing treatment<br>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<br>Difference: | 704 per 1000<br>**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**<br>End of follow-up<br>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<br>Difference: | 570 per 1000<br>**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**<br>During treatment<br>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<br>Difference: | 161 per 1000<br>**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**<br>Within 28 days of commencing treatment<br>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<br>Difference: | 713 per 1000<br>**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**<br>Days<br>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**<br>Days<br>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 low/hi flow, SOLIDARITY 2020 no O2, Beigel 2020 no O2, Beigel 2020 lo-flow, Spinner 2020, Wang 2020 low flow. **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 Inv vent, SOLIDARITY 2020 ventilation, Wang 2020 high flow or ventilation, Beigel 2020 hi flow or NIV. **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, Wang 2020, Spinner 2020, Beigel 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: Wang 2020, Beigel 2020, Wang 2020, Beigel 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, Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020, Wang 2020, Beigel 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: Wang 2020, Beigel 2020, Spinner 2020, Spinner 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: Wang 2020, Spinner 2020, Beigel 2020, Spinner 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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25. Pan H., Peto R., Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V., Abdool Karim Q., et al. : Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med 2020; Journal

26. Spinner CD, Gottlieb RL, Criner GJ, Arribas L?pez 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

27. Wang Y., Zhang D., Du G., Du R., Zhao J., Jin Y., et al. : Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236):1569-1578 Journal

29. Remdesivir for COVID-19. 2020;

## 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 | 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** | **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 |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Remdesivir 10 days | **Intervention** Remdesivir 5 days | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| 9 Critical | | | **1000** ( CI 95% 35 fewer — 19 more ) | | 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 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** | 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 |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Remdesivir 10 days | **Intervention** Remdesivir 5 days | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| | | | ( CI 95% 106 fewer — 20 more ) | | compared to 10-day treatment. |
| **Discontinued due to adverse event** Within 14 days of commencing treatment<br>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<br>Difference: | 33 per 1000<br>**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<br>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<br>Difference: | 676 per 1000<br>**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<br>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<br>Difference: | 893 per 1000<br>**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: Spinner 2020, Goldman 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: Spinner 2020, Goldman 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: Goldman 2020, Spinner 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.**

### References

22. Remdesivir for COVID-19 internal meta-analyses.

24. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R., Montejano R., et al. : Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020; Journal

26. Spinner CD, Gottlieb RL, Criner GJ, Arribas L?pez 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

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 | Biegel 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 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<br>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<br>Difference: | 65 per 1000<br>**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<br>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<br>Difference: | 298 per 1000<br>**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<br>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<br>Difference: | 128 per 1000<br>**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<br>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<br>Difference: | 190 per 1000<br>**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<br>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<br>Difference: | 113 per 1000<br>**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. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo or standard care | **Intervention** Remdesivir | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **Patients requiring ventilation** [14] Within 28 days of commencing treatment<br>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<br>Difference: | 118 per 1000<br>**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<br>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<br>Difference: | 10 per 1000<br>**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<br>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<br>Difference: | 704 per 1000<br>**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<br>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<br>Difference: | 570 per 1000<br>**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<br>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<br>Difference: | 161 per 1000<br>**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<br>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<br>Difference: | 713 per 1000<br>**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 | Hazard Ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 patients in 2 | | | **Moderate** Due to serious risk of bias [28] | Two studies found a statistically significant decrease in time to recovery 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 | studies. [27] (Randomized controlled) | | | | 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 low/hi flow, SOLIDARITY 2020 no O2, Beigel 2020 no O2, Beigel 2020 lo-flow, Spinner 2020, Wang 2020 low flow. **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 Inv vent, SOLIDARITY 2020 ventilation, Wang 2020 high flow or ventilation, Beigel 2020 hi flow or NIV. **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, Wang 2020, Spinner 2020, Beigel 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: Wang 2020, Beigel 2020, Wang 2020, Beigel 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, Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020, Wang 2020, Beigel 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: Wang 2020, Beigel 2020, Spinner 2020, Spinner 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: Wang 2020, Spinner 2020, Beigel 2020, Spinner 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.**

### References

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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 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 | 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. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Remdesivir 10 days | **Intervention** Remdesivir 5 days | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| | | | — 25 more ) | | |
| Clinical recovery<br>Within 14 days of commencing treatment<br>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<br>Difference: | 646 per 1000<br>**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<br>End of follow-up<br>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<br>Difference: | 616 per 1000<br>**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<br>Within 14 days of commencing treatment<br>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<br>Difference: | 33 per 1000<br>**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<br>Within 14 days of commencing treatment<br>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<br>Difference: | 676 per 1000<br>**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<br>Within 28 days of commencing treatment<br>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<br>Difference: | 893 per 1000<br>**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: Spinner 2020, Goldman 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: Spinner 2020, Goldman 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: Goldman 2020, Spinner 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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## 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

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 COVD-19. In addition, less serious adverse events are likely to be of particular importance to people with COVD-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. Certainly 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. Certainly 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]** | Relative risk 1.01 (CI 95% 0.46 — 2.2) Based on data from 450 | **50** per 1000 | **51** per 1000 | **Moderate** Due to serious imprecision [2] | One study found no statistically significant difference in mortality at |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard care or placebo | **Intervention** Tocilizumab | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| Day 14 after commencing treatment<br>9 Critical | patients in 1 studies. [1] (Randomized controlled) | Difference: | **1 more per 1000** ( CI 95% 27 fewer — 60 more ) | | 14 days with tocilizumab compared with control |
| **All-cause mortality [All patients]** Day 21-28 after commencing treatment<br>9 Critical | Relative risk 0.9 (CI 95% 0.83 — 0.98) Based on data from 6,182 patients in 9 studies. [3] (Randomized controlled) | 278 per 1000<br>Difference: | 250 per 1000<br>**28 fewer per 1000** ( CI 95% 47 fewer — 6 fewer ) | **High** | The pooled estimate of nine studies found that tocilizumab decreased death in hospitalised patients at 21 to 28 days compared with control |
| **All-cause mortality [All patients]** Day 60 after commencing treatment<br>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<br>Difference: | 77 per 1000<br>**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<br>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<br>Difference: | 246 per 1000<br>**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<br>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<br>Difference: | 180 per 1000<br>**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<br>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<br>Difference: | 537 per 1000<br>**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** | Based on data from: 1,352 patients in 1 studies. (Randomized | Median adjusted odds ratio 1.46 (95% CI 1.13 - 1.88) | | **Moderate** Because of serious risk of bias | One study that had an ordinal scale combining in-hospital mortality at |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard care or placebo | **Intervention** Tocilizumab | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **mortality and days free of organ support** In hospital mortality at day 90 and days free of organ support at day 21<br>4 Important | controlled) | | | due to lack of blinding [12] | 90 days and days free of organ support to 21 days favoured tocilizumab compared with usual care |
| **Days free of organ support in survivors** Day 21 after commencing treatment<br>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 reviewwith 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 reviewwith 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 reviewwith included studies: [96], [97]. **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: Wang 2020, [97], Soin 2021, Rosas 2020, [96], Stone 2020, Veiga 2021, Hermine 2020, Salama 2020. **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: Veiga 2021, Hermine 2020, Wang 2020, Salama 2020, Stone 2020, [96], Rosas 2020, [41]. **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

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 accessing 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 rick 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<br>9 Critical | 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<br>Difference: | 274 per 1000<br>**37 fewer per 1000** ( CI 95% 90 fewer — 31 more ) | 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 COVID-19 |
| All-cause mortality [All patients] Within 60 days of commencing treatment<br>9 Critical | 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<br>Difference: | 301 per 1000<br>**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 |
| All-cause mortality [All patients] Within 90 days of commencing treatment<br>9 Critical | Relative risk 0.89 (CI 95% 0.74 — 1.06) Based on data from 889 patients in 1 studies. (Randomized controlled) | 370 per 1000<br>Difference: | 329 per 1000<br>**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 |
| Serious adverse events Day 60 to day 90<br>6 Important | 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<br>Difference: | 210 per 1000<br>**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 |
| Adverse events Within 60 days of commencing treatment<br>6 Important | Relative risk 1.01 (CI 95% 0.85 — 1.2) Based on data from 416 patients in 1 studies. (Randomized controlled) | 667 per 1000<br>Difference: | 674 per 1000<br>**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 |
| Ordinal scale combining in-hospital mortality and days free of organ support [9] In-hospital mortality at 90 days and days free of organ | 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 |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard care | **Intervention** Sarilumab | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| support to day 21<br>6 Important | | | | | |
| **Days free of organ support in survivors** Days free of organ support in survivors to 21 days | Based on data from: 887 patients in 1 studies. (Randomized controlled) | Sarilumab (median): 15 days (IQR 9 – 18); usual care: 13 days (IQR 4 – 17) | | **Moderate** Because of serious risk of bias due to lack of blinding [11] | One study found that 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 reviewwith included studies: [127], [126]. **Baseline/comparator:** Systematic review.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Due to serious imprecision.
3. Systematic reviewwith included studies: [126], [127]. **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 reviewwith 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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43. Lescure F-X, Honda H, Fowler RA, Sloane Lazar J, Shi G, Wung P, et al. : Sarilumab treatment of hospitalised patients with severe or critical COVID-19: a multinational, randomised, adaptive, phase 3, double-blind, placebo-controlled trial. medRxiv 2021; 2021020121250769 Journal Website

97. Derde L : Effectiveness of Tocilizumab, Sarilumab, and Anakinra for critically ill patients with COVID-19: The REMAP-CAP COVID-19 Immune Modulation Therapy Domain Randomized Clinical Trial. medRxiv 2021; Journal Website

126. Sivapalasingam S : A Randomized Placebo-Controlled Trial of Sarilumab in Hospitalized Patients with Covid-19. medRxiv 2021; Journal Website

127. Lescure F-X, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, et al. : Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. Respiratory medicine 2021;9(5):522-532 Pubmed Journal

## 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

**Benefits and harms** Small net benefit, or little difference between alternatives

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.

**Certainty of the Evidence** Low

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.

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) 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 days of starting treatment<br>9 Critical | Relative risk 0.98 (CI 95% 0.9 — 1.06) Based on data from 8,271 patients in 3 studies. [1] (Randomized controlled) | 228 per 1000<br>Difference: | 223 per 1000<br>**5 fewer per 1000** ( CI 95% 23 fewer — 14 more ) | Moderate Due to serious imprecision [2] | A pooled analysis of 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. |
| All-cause mortality Within 15 days of starting treatment<br>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<br>Difference: | 175 per 1000<br>**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<br>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<br>Difference: | 86 per 1000<br>**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<br>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<br>Difference: | 110 per 1000<br>**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<br>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<br>Difference: | 16 per 1000<br>**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<br>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<br>Difference: | 617 per 1000<br>**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 |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard care | **Intervention** Azithromycin | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **Discharge from hospital** Within 15 days of starting treatment<br>6 Important | Relative risk 0.92 (CI 95% 0.82 — 1.02) Based on data from 728 patients in 2 studies. [13] (Randomized controlled) | 520 per 1000<br>Difference: | 478 per 1000<br>**42 fewer per 1000** ( CI 95% 94 fewer — 10 more ) | **Very low** Due to serious inconsistency, serious risk of bias, serious indirectness and to serious imprecision [14] | A pooled analysis of 2 studies found no significant difference for discharge from hospital at 15 days with azithromycin compared with standard care for people who were hospitalised |
| **ICU admission** During treatment<br>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<br>Difference: | 36 per 1000<br>**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<br>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<br>Difference: | 394 per 1000<br>**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<br>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 |

1. Systematic review [1] with included studies: Furtado 2020 (COALITION II), Horby 2020 (RECOVERY), Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
3. Systematic review [1] with included studies: Furtado 2020 (COALITION II), Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **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.**
5. Systematic review [1] with included studies: Horby 2020 (RECOVERY). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
7. Systematic review [1] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **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.**
9. Systematic review [1] with included studies: Horby 2020 (RECOVERY), Furtado 2020 (COALITION II), Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **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.**

11. 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: Furtado 2020 (COALITION II), Cavalcanti 2020. **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.**

### References

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<br><br>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<br><br>Difference: | 1 per 1000<br><br>**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** | Relative risk 0.92 (CI 95% 0.59 — 1.43) Based on data from 1,615 patients in 2 | 46 per 1000 | 42 per 1000 | **Low** Due to serious risk of bias and | A pooled analysis of 2 studies found no significant difference for hospitalisation or death |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard care | **Intervention** Azithromycin | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **patients** [3] Within 28 days of starting treatment<br>9 Critical | studies. [4] (Randomized controlled) | Difference: | **4 fewer per 1000** ( CI 95% 19 fewer — 20 more ) | serious imprecision [5] | with azithromycin compared with standard care for people who were managed as outpatients |
| **Hospitalisation or death (composite) - SARS-CoV-2 positive population** [6] Within 28 days of starting treatment<br>9 Critical | 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<br>Difference: | 59 per 1000<br>**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. |
| **NIV/IMV or death (composite)** Within 28 days of starting treatment<br>9 Critical | 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<br>Difference: | 14 per 1000<br>**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. |
| **Invasive mechanical ventilation or ECMO** Within 28 days of starting treatment<br>9 Critical | 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<br>Difference: | 4 per 1000<br>**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. |
| **Virologic clearance** 6 days<br>6 Important | 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<br>Difference: | 106 per 1000<br>**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. |
| **Virologic clearance** 14 days<br>6 Important | 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<br>Difference: | 202 per 1000<br>**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. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard care | **Intervention** Azithromycin | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **Patient reported clinical recovery - All patients** Within 28 days of starting treatment<br>6 Important | Relative risk 1.05 (CI 95% 0.99 — 1.11) Based on data from 1,323 patients in 1 studies. [17] (Randomized controlled) | 767 per 1000<br>Difference: | 805 per 1000<br>**38 more per 1000** ( CI 95% 8 fewer — 84 more ) | **Very low** Due to very serious risk of bias and serious imprecision [18] | 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. |
| **Patient reported clinical recovery - SARS-CoV-2 positive popualtion** Within 28 days of starting treatment<br>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<br>Difference: | 732 per 1000<br>**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<br>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<br>Difference: | 632 per 1000<br>**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<br>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<br>Difference: | 6 per 1000<br>**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<br>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<br>Difference: | 20 per 1000<br>**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: Hinks 2021, Butler 2021 (PRINCIPLE). **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.**

## References

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

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<br>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<br>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<br>9 Critical | Relative risk 0.94 (CI 95% 0.44 — 1.98) Based on data from 1,560 patients in 1 studies. [3] | 18 per 1000<br>Difference: | 17 per 1000<br>**1 fewer per 1000** ( CI 95% 10 fewer — 18 more ) | 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<br>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) | 3 per 1000<br>Difference: | 4 per 1000<br>**1 more per 1000** ( CI 95% 2 fewer — 17 more ) | 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]<br>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<br>9 Critical | 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<br>Difference: | 27 per 1000<br>**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. |
| COVID-19-related urgent care visits, including emergency department assessment or hospitalisation [SARs-CoV-2 positive only] Within 14 days of starting treatment<br>9 Critical | 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<br>Difference: | 15 per 1000<br>**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. |
| Hospital assessment without admission [SARS-CoV-2 positive only] Within 28 days of starting treatment<br>9 Critical | 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<br>Difference: | 28 per 1000<br>**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. |
| ICU admission [SARS-CoV-2 positive only] Within 28 days of starting treatment<br>6 Important | 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<br>Difference: | 13 per 1000<br>**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. |

| **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<br>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<br>Difference: | 64 per 1000<br>**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<br>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<br>Difference: | 586 per 1000<br>**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]<br>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<br>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<br>Difference: | 840 per 1000<br>**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]<br>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<br>Difference: | 783 per 1000<br>**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<br>6 Important | 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<br>Difference: | 901 per 1000<br>**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. |
| Time to alleviation of all symptoms [SARS-CoV-2 positive only]<br>6 Important | 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. |
| 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.**

### References

92. Inhaled budesonide for COVID-19.

94. Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. : Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. The Lancet. Respiratory medicine 2021;9(7):763-772 Pubmed Journal

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

Updated

Do not use colchicine to treat COVID-19.

## Evidence To Decision

### Benefits and harms

Important harms

#### Hospital settings

The panel considered that the results from studies of colchicine for COVID-19 in hospitals showed no benefit of effect on all-cause mortality, mechanical ventilation, discontinuation due to adverse events, clinical progression, ICU admission, or discharge from hospital within 28 days.

The evidence shows that people having colchicine plus standard care have statistically significantly more adverse events compared with people having standard care alone. Known adverse effects such as diarrhoea appear to have been under-reported in the identified evidence in hospital settings. The panel noted that colchicine commonly causes diarrhoea, which can lead to potassium deficiency (hypokalaemia). They advised that, because of the adverse events, colchicine tends to be used (for the treatment of gout) only for 3 to 4 days.

Although one study suggests that colchicine plus standard care reduces duration of hospital stay at a mean follow-up of 21 days compared with placebo plus standard care, this reduction of hospital stay is not statistically significant (a mean difference of 1.84 days (95% CI 0.78 to 2.90)).

#### Community settings

The panel considered that the results from studies of colchicine for COVID-19 in the community showed no benefit on hospitalisation for COVID-19, all-cause mortality, all-cause mortality or hospitalisation, mechanical ventilation, number of participants who experienced alleviation of all symptoms, or reported recovery time.

The evidence shows that people having colchicine plus standard care have a statistically significant reduction in serious adverse events compared with standard care alone or with placebo. This is possibly because pneumonia was reported less frequently in patients of the colchicine group compared with those in the placebo group. However, people having colchicine plus standard care have a statistically significant increase in adverse events compared with standard care plus placebo. The adverse event diarrhoea was higher with colchicine than with placebo in Tardif 2021.

### Certainty of the Evidence

Very low

The panel agreed that the certainty of evidence on colchicine for people with COVID-19 in hospital and in the community ranges from high to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with most studies having some degree of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care in hospitals not including corticosteroids); 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). Two studies were only available as preprints.

### 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

Important issues, or potential issues not investigated

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

Colchicine costs from £2.54 for 28 tablets (BNF, November 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**

Important issues, or potential issues not investigated

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, both in hospital and community settings, shows no beneficial effect on all-cause mortality or need for mechanical ventilation compared with standard care. It also shows no effect on duration of hospital stay or hospitalisation. The evidence also shows that colchicine causes statistically significantly more adverse events than standard care within 21 days of starting treatment in hospital or 30 days in the community. There is no evidence for children or young people. Therefore, colchicine should not be used to treat COVID-19 in people of any age.

## Clinical Question/ PICO

**Population:** People with COVID-19 in hospital
**Intervention:** Colchicine
**Comparator:** Placebo or standard care

## Summary

There is no evidence that colchicine is more effective than placebo or standard care in treating hospitalised patients with COVID-19.

**What is the evidence informing this conclusion?**
This is a November 2021 update of the evidence review from May 2021 and includes 1 new study (RECOVERY 2021). Evidence comes from 4 randomised trials that compared colchicine with placebo or standard care in 11620 adults admitted to hospital with COVID-19 (Deftereos 2020, Lopes 2021, Salehzadeh 2020, RECOVERY 2021).

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.

**Publication status**
Salehzadeh 2020 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 Deftereos 2020, an arterial oxygen partial pressure of lower than 95 mmHg on room air was a key inclusion criterion. Lopes 2021 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 2020 did not define disease severity other than specifying COVID-19 with confirmed lung involvement. In RECOVERY 2021, 15% of participants had no oxygen support or simple oxygen, 31-33% had non-invasive ventilation, and 45-46% had invasive mechanical ventilation.

The dosage of colchicine differed across the studies. Deftereos 2020, RECOVERY 2021, and Lopes 2021 used a higher initial dose (from 1,000 micrograms daily to 2,000 micrograms daily) for between 1 and 5 days before switching to a lower maintenance dose. The daily dose in the maintenance phase was 1,000 micrograms (Deftereos 2020, RECOVERY 2021, Lopes 2021, Salehzadeh 2020). Duration of treatment ranged from 6 days to 3 weeks across the studies.

Participants in 3 studies received hydroxychloroquine (or chloroquine) and azithromycin as part of standard care (Deftereos 2020, Lopes 2021, Salehzadeh 2020 ). Deftereos 2020 compared colchicine with standard care which included using hydroxychloroquine (or chloroquine) in 98% of participants and azithromycin in 92% of participants. RECOVERY 2021 compared colchicine with standard care which included using corticosteroids in 93% of participants and remdesivir in 22% of participants.

Follow-up ranged from 2 to 3 weeks; however Lopes 2021 did not clearly report the duration of follow-up.

Pregnant and breastfeeding women were excluded from all studies. No children were included.

For further details see the evidence review.

**What are the main results?**
**Critical outcomes**

There was no statistically significant effect on mortality or need for mechanical ventilation within 21 to 28 days of starting colchicine treatment compared with placebo or standard care.

**Important outcomes**

There was a statistically significant increase in adverse events with colchicine compared with standard care.

No statistically significant differences were seen with colchicine compared with control for the other important outcomes reviewed. This includes duration of hospital stay.

**Our confidence in the results**
The certainty of evidence is moderate to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with all studies having some degree of risk of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care not including corticosteroids); 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). One study was only available as a preprint.

| **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<br><br>9 Critical | Relative risk 0.66 (CI 95% 0.24 — 1.85) Based on data from 11,517 patients in 3 studies. [1] | 206 per 1000<br><br>Difference: | 136 per 1000<br><br>**70 fewer per 1000** ( CI 95% 157 fewer — 175 | **Moderate** Due to serious imprecision [2] | The pooled estimate of three studies found no statistically significant difference in all-cause mortality at 21 to 28 days, and at an unspecified timepoint with colchicine |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo or standard care | **Intervention** Colchicine | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| | | | more ) | | compared with control |
| Mechanical ventilation within 21-28 days of starting treatment<br>9 Critical | Relative risk 0.53 (CI 95% 0.09 — 3.15) Based on data from 10,916 patients in 2 studies. [3] | 244 per 1000<br>Difference: | 129 per 1000<br>**115 fewer per 1000** ( CI 95% 222 fewer — 525 more ) | Very low<br>Because of serious risk of bias due to lack of blinding, and due to serious imprecision, serious inconsistency, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen [4] | The pooled estimate of two studies found no statistically significant difference in mechanical ventilation at 21 to 28 days with colchicine compared with control |
| Serious adverse events within 21 days of starting treatment<br>6 Important | Relative risk<br>Based on data from 105 patients in 1 studies. | 0 per 1000 | CI 95% | Moderate<br>Because of serious risk of bias due to lack of blinding, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen [5] | One study found there were no serious adverse events at 3 weeks for either colchicine or standard care |
| Adverse events within 21 days of starting treatment<br>6 Important | Relative risk 2.61 (CI 95% 1.67 — 4.07) Based on data from 105 patients in 1 studies. [6] | 300 per 1000<br>Difference: | 783 per 1000<br>**483 more per 1000** ( CI 95% 201 more — 921 more ) | Low<br>Because of serious risk of bias due to lack of blinding, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen [7] | One study found that there was a statistically significant increase in adverse events with colchicine compared with standard care within 21 days of starting treatment |
| Discontinuation due to adverse events within 21 days of starting treatment<br>6 Important | Relative risk 4.55 (CI 95% 0.22 — 92.62) Based on data from 177 patients in 2 studies. [8] | 0 per 1000<br>Difference: | 0 per 1000<br>**0 fewer per 1000** ( CI 95% 0 fewer — 0 fewer ) | Very low<br>Because of serious bias due to lack of blinding, and due to very serious imprecision with fewer than 300 participants, and due to indirectness | The pooled estimate of two studies found no statistically significant difference in discontinuation due to adverse events with colchicine compared with 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** |
|---|---|---|---|---|---|
| | | | | because standard care did not include dexamethasone for hospitalised patients on oxygen [9] | |
| **Clinical progression (scale)** within 21 days of starting treatment. Increase of 2 grades on 7-grade scale<br><br>6 Important | Relative risk 0.13 (CI 95% 0.02 — 1.02) Based on data from 105 patients in 1 studies. [10] | 140 per 1000<br><br>Difference: | 18 per 1000<br><br>**122 fewer per 1000** ( CI 95% 137 fewer — 3 more ) | **Very low** Because of serious bias due to lack of blinding, and due to very serious imprecision with fewer than 300 participants, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen [11] | One study found a non-statistically significant reduction in clinical progression with colchicine compared with standard care |
| **ICU admission** follow-up timepoint was not provided<br><br>6 Important | Relative risk 0.33 (CI 95% 0.04 — 3.06) Based on data from 72 patients in 1 studies. [12] | 83 per 1000<br><br>Difference: | 27 per 1000<br><br>**56 fewer per 1000** ( CI 95% 80 fewer — 171 more ) | **Very low** Because of serious bias due to lack of specified follow-up timepoints, and due to very serious imprecision with fewer than 300 participants [13] | One study found no statistically significant difference in ICU admission with colchicine compared with placebo |
| **Discharge from hospital** by day 10<br><br>6 Important | Relative risk 1.5 (CI 95% 1.14 — 1.98) Based on data from 72 patients in 1 studies. [14] | 611 per 1000<br><br>Difference: | 917 per 1000<br><br>**306 more per 1000** ( CI 95% 86 more — 599 more ) | **Moderate** Because of serious bias due to lack of specified follow-up timepoints [15] | One study found that more people were discharged from hospital by day 10 in the colchicine arm compared with placebo |
| **Discharge from hospital** within 28 days<br><br>6 Important | Relative risk 0.99 (CI 95% 0.96 — 1.01) Based on data from 11,340 patients in 1 studies. [16] (Randomized controlled) | 704 per 1000<br><br>Difference: | 697 per 1000<br><br>**7 fewer per 1000** ( CI 95% 28 fewer — 7 more ) | **Low** Because of serious bias due to lack of blinding, and due to serious imprecision [17] | One study found no statistically significant difference in discharge from hospital within 28 days with colchicine compared with standard care |
| **Duration of hospital stay** at a mean follow- | Based on data from: 100 | Difference: | **MD 1.84 lower** ( CI 95% 2.9 lower — 0.78 lower ) | **Very low** Because of very serious bias due | One study found that the duration of hospital stay was less with |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo or standard care | **Intervention** Colchicine | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| up of 21 days (mean difference)<br><br>6 Important | patients in 1 studies. [18] | | | to randomisation method not being provided, lack of blinding, and due to selective reporting of outcomes, and due to indirectness because standard care did not include corticosteroids for hospitalised patients on oxygen [19] | colchicine compared with standard care at a mean follow-up of 21 days |

1. Systematic review [142] with included studies: Lopes 2021, GRECCO-19 2020, RECOVERY 2021. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [46], [47], [146],
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
3. Systematic review [142] with included studies: RECOVERY 2021, GRECCO-19 2020. **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: serious.** The magnitude of statistical heterogeneity was high, with I^2:... %.. **Indirectness: serious.** Standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
5. **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.** standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: no serious. Publication bias: no serious.**
6. Systematic review [142] with included studies: GRECCO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
7. **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.** standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: no serious. Publication bias: no serious.**
8. Systematic review [142] with included studies: Lopes 2021, GRECCO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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: serious.** standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: very serious.** Wide confidence intervals, Low number of patients. **Publication bias: no serious.**
10. Systematic review [142] with included studies: GRECCO-19 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. **Indirectness: serious.** standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: very serious.** Wide confidence intervals, Low number of patients.
12. Systematic review [142] with included studies: Lopes 2021. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Risk of Bias: serious.** Because of serious bias due to lack of specified follow-up timepoints. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients. **Publication bias: no serious.**

14. Systematic review [142] with included studies: Lopes 2021. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Risk of Bias: serious.** Lack of specified follow-up timepoints. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
16. Systematic review [142] with included studies: RECOVERY 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
18. Systematic review [142] with included studies: Salehzadeh 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [48],
19. **Risk of Bias: very serious.** Due to randomisation method not being provided, lack of blinding, and due to selective reporting of outcomes. **Inconsistency: no serious. Indirectness: serious.** Because standard care did not include corticosteroids for hospitalised patients on oxygen. **Imprecision: no serious. Publication bias: no serious.**

### References

46. Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, et al. : Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. JAMA network open 2020;3(6):e2013136 Pubmed Journal

47. Lopes MI, Bonjorno LP, Giannini MC, Amaral NB, Menezes PI, Dib SM, et al. : Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. RMD open 2021;7(1): Pubmed Journal

48. Salehzadeh F, Pourfarzi F, Ataei S : The Impact of Colchicine on The COVID-19 Patients; A Clinical Trial Study. Research Square 2020; Journal Website

142. Colchicine for COVID-19 in hospitals - November 2021.

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## Clinical Question/ PICO

**Population:** People with COVID-19 in the community
**Intervention:** Colchicine
**Comparator:** Placebo

### Summary

There is no evidence that colchicine is more effective than placebo or standard care in treating patients in the community with COVID-19.

**What is the evidence informing this conclusion?**
This is a November 2021 update of an evidence review from May 2021 and includes 1 new study (PRINCIPLE 2021). Evidence comes from 2 randomised trials that compared colchicine with placebo or standard care in 4764 adults in the community with COVID-19 (Tardiff 2021 (COLCORONA trial), PRINCIPLE 2021).

**Publication status**
PRINCIPLE 2021 was only available as a preprint and has therefore not been peer reviewed.

**Study characteristics**
The age of participants ranged from 18 to over 65 years and the proportion of women ranged from 49 to 59%. The studies did not clearly define the severity of COVID-19.

For Tardif 2021, the dosage of colchicine was 500 micrograms twice daily for the first 3 days then once daily for 27 days. For PRINCIPLE 2021, participants received colchicine 500 micrograms daily for 14 days.

As standard care in PRINCIPLE 2021, participants received medications focused on managing symptoms with antipyretics. In Tardif 2021, small percentages of participants were given hydroxychloroquine, oral anticoagulants, aspirin, and/or other platelet agents.

Follow-up after starting treatment was 28 days for PRINCIPLE 2021 and 30 days for Tardif 2021.

Pregnant and breastfeeding women were excluded from all studies. No children were included.

For further details see the evidence review.

**What are the main results?**
**Critical outcomes**

For the critical outcomes of hospitalisation for COVID-19, all-cause mortality, and need for mechanical ventilation, there was no statistically significant effect 28-30 days after starting colchicine treatment compared with control.

**Important outcomes**

There was a statistically significant increase in adverse events with colchicine compared with standard care. There was a statistically significant increase in serious adverse events with standard care compared with colchicine. This was potentially due to a greater number of cases of pneumonia in the standard care arm.

No statistically significant differences were seen with colchicine compared with control for the other important outcomes reviewed. This includes time to reported recovery.

**Our confidence in the results**
The certainty of evidence is high to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with one study having some degree of risk of bias); inconsistency (for example, when point estimates varied widely between studies); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect). One study was only available as a preprint.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Colchicine | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **Hospitalisation for COVID-19** within 30 days of starting treatment<br>9 Critical | Relative risk 0.8 (CI 95% 0.62 — 1.03) Based on data from 4,488 patients in 1 studies. [1] (Randomized controlled) | 57 per 1000<br>Difference: | 46 per 1000<br>**11 fewer per 1000** ( CI 95% 22 fewer — 2 more ) | **Moderate** Due to serious imprecision [2] | One study found no statistically significant difference in hospitalisation for COVID-19 at 30 days with colchicine compared with placebo |
| **All-cause mortality** within 30 days of starting treatment<br>9 Critical | Relative risk 0.56 (CI 95% 0.19 — 1.67) Based on data from 4,488 patients in 1 studies. [3] | 4 per 1000<br>Difference: | 2 per 1000<br>**2 fewer per 1000** ( CI 95% 3 fewer — 3 more ) | **Moderate** Due to serious imprecision [4] | One study found no statistically significant difference in mortality at 30 days with colchicine compared with placebo |
| **All-cause mortality or hospitalisation** (28 or 30 days) | Relative risk 0.83 (CI 95% 0.65 — 1.06) Based on data from 4,764 patients in 2 studies. [5] | 56 per 1000<br>Difference: | 46 per 1000<br>**10 fewer per 1000** | **Moderate** Due to serious imprecision [6] | Two studies found a non-significant reduction in all-cause mortality or hospitalisation at 28 to 30 days with colchicine compared with control |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Colchicine | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| 9 Critical | | | ( CI 95% 20 fewer — 3 more ) | | |
| Mechanical ventilation within 28-30 days of starting treatment<br>6 Important | Relative risk 0.53 (CI 95% 0.26 — 1.09) Based on data from 4,763 patients in 2 studies. [7] | 9 per 1000<br>Difference: | 5 per 1000<br>**4 fewer per 1000** ( CI 95% 7 fewer — 1 more ) | Moderate Due to serious imprecision [8] | The pooled estimate of two studies found a non-statistically significant reduction in mechanical ventilation at 28 to 30 days with colchicine compared with control |
| Serious adverse events within 28-30 days of starting treatment<br>6 Important | Relative risk 0.78 (CI 95% 0.61 — 0.99) Based on data from 4,688 patients in 2 studies. [9] | 60 per 1000<br>Difference: | 47 per 1000<br>**13 fewer per 1000** ( CI 95% 23 fewer — 1 fewer ) | High | The pooled estimate of two studies found a statistically significant reduction in serious adverse events in the colchicine arm at day 28 or day 30 compared with control |
| Adverse events within 30 days of starting treatment<br>6 Important | Relative risk 1.56 (CI 95% 1.38 — 1.76) Based on data from 4,412 patients in 1 studies. [10] | 155 per 1000<br>Difference: | 242 per 1000<br>**87 more per 1000** ( CI 95% 59 more — 118 more ) | High | One study found a statistically significant increase in adverse events in the colchicine arm at day 30 compared with placebo |
| Participants who experienced alleviation of all symptoms within 28 days of starting treatment<br>6 Important | Relative risk 1 (CI 95% 0.92 — 1.1) Based on data from 252 patients in 1 studies. [11] | 883 per 1000<br>Difference: | 883 per 1000<br>**0 fewer per 1000** ( CI 95% 71 fewer — 88 more ) | Very low Because of serious risk of bias due to a high dropout rate, concerns with randomisation, and lack of blinding, and due to serious imprecision [12] | One study found no statistically significant difference in the number of participants who experienced alleviation of all symptoms within 28 days of starting treatment with colchicine and standard care compared with standard care |
| Reported recovery (days) within 28 days of starting treatment<br>6 Important | Odds Ratio 0.92 (CI 95% 0.72 — 1.17) Based on data from 276 patients in 1 studies. (Randomized controlled) | | CI 95% | Very low Because of serious risk of bias due to a high dropout rate, concerns with randomisation, lack of blinding, and due to serious imprecision [13] | One study found no statistically significant difference in reported recovery with colchicine plus standard care compared with standard care alone |
| Time to alleviation of all symptoms estimated | Based on data from: 252 patients in 1 studies. [14] | Difference: | **MD 0.94 higher** ( CI 95% 0.68 higher — 1.2 higher ) | Low Because of serious risk of bias due to a high | One study found that alleviation of all symptoms happened sooner with colchicine |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Colchicine | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| treatment effect (median days) within 28 days of starting treatment, mean difference<br><br>6 Important | (Randomized controlled) | | | dropout rate, concerns with randomisation, and lack of blinding [15] | and standard care compared with standard care |
| **Time to reported recovery, median difference in days** within 28 days of starting treatment, median difference<br><br>6 Important | Based on data from: 276 patients in 1 studies. (Randomized controlled) | Median difference: 1.14 (95 CI -1.86 to 5.21). A positive value in estimated median difference in time to recovery corresponds to an increase in time to recovery in days in colchicine compared with standard care | | **Very low** Because of serious risk of bias due to a high dropout rate, concerns with randomisation, lack of blinding, and due to serious imprecision [16] | One study found no statistically significant difference in time to reported recovery with colchicine plus standard care compared with standard care alone |

1. Systematic review [143] with included studies: COLCORONA 2021. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [49],
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
3. Systematic review [143] with included studies: COLCORONA 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
5. Systematic review [143] with included studies: COLCORONA 2021, PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [147], [49],
6. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.** Due to serious imprecision. **Publication bias: no serious.**
7. Systematic review [143] with included studies: COLCORONA 2021, PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
9. Systematic review [143] with included studies: COLCORONA 2021, PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [143] with included studies: COLCORONA 2021. **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [143] with included studies: PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** due to a high dropout rate, concerns with randomisation, and lack of blinding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
13. **Risk of Bias: very serious.** Because of serious risk of bias due to a high dropout rate, concerns with randomisation, lack of blinding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
14. Systematic review [143] with included studies: PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Risk of Bias: very serious.** Due to a high dropout rate, concerns with randomisation, and lack of blinding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

16. **Risk of Bias: very serious.** because of serious risk of bias due to a high dropout rate, concerns with randomisation, lack of blinding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**

### References

49. Tardif JC, Bouabdallaoui N, L'Allier PL, Gaudet D : Efficacy of Colchicine in Non-Hospitalized Patients with COVID-19. medRxiv 2021; Journal Website

143. Colchicine for COVID-19 in the community - November 2021.

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## 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/m$^2$.) 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 6 Important | 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. |
| Sustained alleviation of all symptoms Within 28 days 6 Important | 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 |
| Sustained recovery Within 28 days 6 Important | 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 |
| Time to initial reduction of severity of symptoms 6 Important | 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 |
| Time to alleviation of all symptoms 6 Important | 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 |

| **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<br>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<br>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<br>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)<br>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<br>Difference: | 9 per 1000<br>**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<br>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<br>Difference: | 16 per 1000<br>**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)<br>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<br>Difference: | 51 per 1000<br>**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)<br>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<br>Difference: | 55 per 1000<br>**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)<br>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<br>Difference: | 5 per 1000<br>**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)<br>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<br>Difference: | 7 per 1000<br>**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)<br>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<br>Difference: | 393 per 1000<br>**34 fewer per 1000** ( CI 95% 77 fewer — 13 more ) | Very low<br>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<br>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<br>Difference: | 33 per 1000<br>**22 more per 1000** ( CI 95% 1 more — 77 more ) | Very low<br>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<br>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<br>Difference: | 7 per 1000<br>**17 fewer per 1000** ( CI 95% 24 fewer — 147 more ) | Very low<br>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<br>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<br>Difference: | 19 per 1000<br>**14 fewer per 1000** ( CI 95% 27 fewer — 30 more ) | Very low<br>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)<br>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<br>Difference: | 820 per 1000<br>**32 more per 1000** ( CI 95% 47 fewer — 118 more ) | Very low<br>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<br>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<br>Difference: | 360 per 1000<br>**40 fewer per 1000** ( CI 95% 224 fewer — 332 more ) | Very low<br>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) | 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<br>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) 6 Important | 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 Difference: | 714 per 1000 **114 more per 1000** ( CI 95% 156 fewer — 546 more ) | 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. |
| Virological clearance (within 14 days) (Buonfrate higher dose) 6 Important | 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 Difference: | 564 per 1000 **36 fewer per 1000** ( CI 95% 264 fewer — 354 more ) | 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 virological clearance for ivermectin compared with control. |
| Recovery (from date of illness onset) 6 Important | 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. |
| Recovery (from date of enrolment) 6 Important | Based on data from: 62 patients in 1 studies. [33] (Randomized controlled) | 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. |

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: Vallejos 2021, Buonfrate 2021 600 ug, Biber 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: Buonfrate 2021 1200 ug, Biber 2021, 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-Elsalam 2021; Ahmed 2021; Bukhari 2021; Gonzalez 2021; Kishoria 2020; Krolewiecki 2021; Mohan 2021; Pott-Junior 2021; Ravikirti 2021; Shahbaznejad 2021; Shakhsi 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-Elsalam 2021; Ahmed 2021; Kishoria 2020; Krolewiecki 2021; Mohan 2021; Pott-Junior 2021; Ravikirti 2021; Shahbaznejad 2021; Shakhsi 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)<br><br>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<br><br>Difference: | 36 per 1000<br><br>**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<br>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<br>Difference: | 81 per 1000<br>**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<br>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<br>Difference: | 29 per 1000<br>**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)<br>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<br>Difference: | 903 per 1000<br>**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)<br>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<br>Difference: | 803 per 1000<br>**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)<br>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<br>Difference: | 0 per 1000<br>**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)<br>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<br>Difference: | 65 per 1000<br>**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<br>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<br>Difference: | 171 per 1000<br>**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)<br>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<br>Difference: | 928 per 1000<br>**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<br>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<br>Difference: | 62 per 1000<br>**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)<br>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<br>Difference: | 485 per 1000<br>**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)<br>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<br>Difference: | 635 per 1000<br>**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)<br>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)<br>Difference: | 6 (Median)<br>**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**<br>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**<br>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)**<br>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**<br>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**<br>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**<br>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.

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### 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 ≤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<br><br>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<br><br>Difference: | 41 per 1000<br><br>**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<br>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<br>Difference: | 101 per 1000<br>**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<br>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<br>Difference: | 161 per 1000<br>**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<br>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<br>Difference: | 927 per 1000<br>**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 hospitalised. |
| Survival to hospital discharge without major thrombotic events<br>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<br>Difference: | 919 per 1000<br>**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. |

| **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<br>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<br>Difference: | 915 per 1000<br>**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 thromboembolism 30 days<br>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<br>Difference: | 9 per 1000<br>**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 thromboembolism - rivaroxaban 30 days<br>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<br>Difference: | 35 per 1000<br>**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<br>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<br>Difference: | 74 per 1000<br>**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<br>9 Critical | Relative risk 1.3 (CI 95% 0.34 — 4.98) Based on data from 2,692 patients in 2 | 10 per 1000<br>Difference: | 13 per 1000<br>**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<br>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<br>Difference: | 32 per 1000<br>**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<br>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<br>Difference: | 980 per 1000<br>**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<br>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<br>Difference: | 52 per 1000<br>**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<br>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<br>Difference: | 145 per 1000<br>**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<br>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<br>Difference: | 92 per 1000<br>**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<br>6 Important | Based on data from: 465 patients in 1 studies. [33] (Randomized controlled) | 24.1 (Mean)<br>Difference: | 25.8 (Mean)<br>**MD 1.7 higher** ( CI 95% 0.32 higher — 3.08 higher ) | Moderate<br>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: RAPID 2021, REMAP-CAP 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<br><br>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<br><br>Difference: | 99 per 1000<br><br>**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<br><br>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<br><br>Difference: | 368 per 1000<br><br>**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 disharge<br><br>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<br><br>Difference: | 626 per 1000<br><br>**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<br>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<br>Difference: | 37 per 1000<br>**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<br>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<br>Difference: | 536 per 1000<br>**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<br>6 Important | High better Based on data from: 20 patients in 1 studies. (Randomized controlled) | 0 (Median) | 15 (Median)<br>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: HESACOVID 2020, REMAP-CAP 2021. **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 enoxoparin (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<br>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<br>Difference: | 367 per 1000<br>**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<br>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<br>Difference: | 460 per 1000<br>**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<br>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<br>Difference: | 24 per 1000<br>**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<br>30 days<br><br>9 Critical | Relative risk 1.02<br>(CI 95% 0.52 — 2)<br>Based on data from 735 patients in 2 studies. [7]<br>(Randomized controlled) | 43<br>per 1000<br><br>Difference: | 44<br>per 1000<br><br>**1 more per 1000**<br>( CI 95% 21 fewer — 43 more ) | Very low<br>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<br>90 days<br><br>9 Critical | Relative risk 0.93<br>(CI 95% 0.38 — 2.26)<br>Based on data from 562 patients in 1 studies. [9]<br>(Randomized controlled) | 35<br>per 1000<br><br>Difference: | 33<br>per 1000<br><br>**2 fewer per 1000**<br>( CI 95% 22 fewer — 44 more ) | Low<br>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<br>30 days<br><br>6 Important | High better<br>Based on data from: 562 patients in 1 studies. (Randomized controlled) | 30<br>(Median) | 30<br>(Median)<br><br>CI 95% | Very low<br>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: Perepu 2021, INSPIRATION 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: Perepu 2021, INSPIRATION 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 ≤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<br><br>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<br><br>Difference: | 919 per 1000<br><br>**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<br><br>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<br><br>Difference: | 915 per 1000<br><br>**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 thromboembolism 30 days<br><br>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<br><br>Difference: | 9 per 1000<br><br>**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 thromboembolism - rivaroxaban 30 days<br><br>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<br><br>Difference: | 35 per 1000<br><br>**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<br><br>Difference: | 74 per 1000<br><br>**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** |
|---|---|---|---|---|---|
| 9 Critical | | | **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 |
| Major bleeding<br>9 Critical | 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<br>Difference: | 13 per 1000<br>**3 more per 1000** ( CI 95% 7 fewer — 40 more ) | Low<br>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. |
| Major bleeding - rivaroxaban<br>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<br>Difference: | 32 per 1000<br>**19 more per 1000** ( CI 95% 3 fewer — 87 more ) | Low<br>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<br>28 days<br>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<br>Difference: | 980 per 1000<br>**226 more per 1000** ( CI 95% 0 fewer — 460 more ) | Moderate<br>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<br>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<br>Difference: | 52 per 1000<br>**42 more per 1000** ( CI 95% 5 more — 168 more ) | Moderate<br>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. |

| **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<br>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<br>Difference: | 145 per 1000<br>**32 fewer per 1000** ( CI 95% 81 fewer — 42 more ) | Moderate<br>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<br>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<br>Difference: | 92 per 1000<br>**18 fewer per 1000** ( CI 95% 56 fewer — 50 more ) | Moderate<br>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<br>6 Important | Based on data from: 465 patients in 1 studies. [33] (Randomized controlled) | 24.1 (Mean)<br>Difference: | 25.8 (Mean)<br>**MD 1.7 higher** ( CI 95% 0.32 higher — 3.08 higher ) | Moderate<br>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: RAPID 2021, REMAP-CAP 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.**

### References

84. Heparins for COVID-19.

85. Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al. : Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. The New England journal of medicine 2021; Pubmed Journal

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141. Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, N? ?inle F, et al. : Heparin for Moderately Ill Patients with Covid-19. medRxiv : the preprint server for health sciences 2021; Journal

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 COVD-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<br><br>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<br><br>Difference: | 99 per 1000<br><br>**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<br><br>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<br><br>Difference: | 368 per 1000<br><br>**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** |
|---|---|---|---|---|---|
| | | | | | (dose and treatment varies) for people who were hospitalised. |
| Survival to hospital disharge<br>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<br>Difference: | 626 per 1000<br>**19 fewer per 1000** ( CI 95% 71 fewer — 39 more ) | Low<br>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 (dose and treatment varies) for people who were hospitalised. |
| Major bleeding<br>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<br>Difference: | 37 per 1000<br>**14 more per 1000** ( CI 95% 4 fewer — 52 more ) | Low<br>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<br>21 days<br>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<br>Difference: | 536 per 1000<br>**46 fewer per 1000** ( CI 95% 100 fewer — 7 more ) | Low<br>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<br>28 days<br>6 Important | High better Based on data from: 20 patients in 1 studies. (Randomized controlled) | 0 (Median) | 15 (Median)<br>CI 95% | Low<br>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: HESACOVID 2020, REMAP-CAP 2021. **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.**

### References

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85. Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al. : Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. The New England journal of medicine 2021; Pubmed Journal

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99. Zarychanski R, Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, et al. : Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. The New England journal of medicine 2021;385(9):777-789 Pubmed Journal

## 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 enoxoparin (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<br>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<br>Difference: | 367 per 1000<br>**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<br>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<br>Difference: | 460 per 1000<br>**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<br>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<br>Difference: | 24 per 1000<br>**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<br>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<br>Difference: | 44 per 1000<br>**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<br>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<br>Difference: | 33 per 1000<br>**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<br>6 Important | High better Based on data from: 562 patients in 1 studies. (Randomized controlled) | 30 (Median) | 30 (Median)<br>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: Perepu 2021, INSPIRATION 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: Perepu 2021, INSPIRATION 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/m$^2$ 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.

# 9. Identifying and managing co-infections

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).

## 9.1 Bacterial pneumonia

### 9.1.1 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.

## 9.1.2 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.

## 9.1.3 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.

### 9.1.4 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.

### 9.1.5 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.

## 9.2 COVID-19-associated pulmonary aspergillosis (CAPA)

New

Info Box

For people who are critically ill and have, or have had, COVID-19 as part of their acute illness:

- CAPA is a recognised cause of someone's condition not improving despite treatment (for example, antibiotic therapy, ventilatory support)
- there are no specific combinations of signs or symptoms for diagnosing CAPA
- the risk of having CAPA may increase with age and chronic lung disease.

### 9.2.1 Diagnosing CAPA

Consensus recommendation

New

When deciding whether to suspect CAPA in someone who is critically ill and has, or has had, COVID-19 as part of their acute illness:

- base your decisions on individual risk factors and the person's clinical condition
- involve a multidisciplinary team, including infection specialists
- refer to local protocols on diagnosing and managing CAPA.

*Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.*

#### Evidence To Decision

| Benefits and harms | Small net benefit, or little difference between alternatives |
| --- | --- |

The panel were presented with evidence from one systematic review (Chong 2021) and two primary studies (Prattes 2021 and Segrelles-Calvo 2021). The studies presented evidence on the risk factors and signs and symptoms associated with people developing CAPA.

The panel agreed that there was insufficient evidence to define specific risk factors or signs and symptoms of CAPA. Although the studies suggest that increasing age and chronic lung disease may increase the risk of developing CAPA, the panel considered that the evidence was not strong enough to include these specific risk factors in a diagnostic recommendation. They also agreed that, while studies suggest that people who receive invasive mechanical ventilation are at increased risk of CAPA, the thresholds for mechanical ventilation vary across centres and invasive mechanical ventilation may not be considered an independent risk factor for CAPA. The panel also considered the evidence around whether taking long-term immunosuppressants can increase the risk of CAPA, but concluded that the evidence was not strong enough to list 'long-term immunosuppressants' as an independent risk factor for CAPA.

The panel highlighted the need to use clinical judgement and assess the individual needs of people who are suspected to have CAPA, before progressing further with their diagnosis and management.

The panel considered whether existing clinical algorithms for the diagnosis of invasive pulmonary aspergillosis could be applied to CAPA. In particular, the panel discussed the AspICU algorithm, which is a clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. However, the panel agreed not to recommend use of the AspICU algorithm for CAPA because of a lack of evidence of its use in this condition and meaningful differences between the people for which the AspICU algorithm is typically used and the people who are at risk of developing CAPA.

The panel discussed that from their experience, a diagnosis of CAPA should usually be made as part of a multidisciplinary team, with input from infection specialists (for example, medical microbiologists or infectious disease specialists).

**Certainty of the Evidence** Very low

The certainty of the evidence was rated as low to very low for all outcomes. This was due to serious risk of bias, serious indirectness, and serious inconsistency. The panel discussed that heterogeneity of the study participants, and the variations in local practice in reporting and case definitions of CAPA also reduced their certainty in the results.

In particular, the panel discussed that the association shown between invasive mechanical ventilation and CAPA is likely to be at risk of bias from confounding due to the difference in diagnostic approach between those who are invasively mechanically ventilated and those who are not.

**Preference and values** No substantial variability expected

The panel were not aware of any systematically collected data about the preferences and values in people who are suspected to have CAPA.

**Resources** Important issues, or potential issues not investigated

No formal analysis of resource impact has been carried out. The panel recommended that decisions about whether to suspect CAPA should be made as part of a multidisciplinary team which includes infection specialists, which may not currently be in place in all settings where people who are critically ill are cared for.

**Equity** Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill and have, or have had, COVID-19 as part of their acute illness.

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 the acceptability of assessing for suspicion of CAPA.

**Feasibility** Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility, but agreed that this approach should be feasible, particularly where a multidisciplinary team which includes infection specialists is already in place.

### Rationale

The panel agreed that the evidence was not strong enough to recommend specific factors that increase the risk of CAPA. They noted the importance of multidisciplinary decision making and using local protocols when deciding whether to suspect CAPA.

## Clinical Question/ PICO

**Population:** Risk factors for People hospitalised with confirmed COVID-19 and CAPA
**Intervention:** People with CAPA
**Comparator:** People without CAPA

### Summary

There remains a high degree of uncertainty over possible risk factors that are associated with people developing COVID-19-associated pulmonary aspergillosis.

**What is the evidence informing this conclusion?**

Evidence comes from 2 studies. The first (Chong 2021) was a systematic review and meta-analysis of cohort studies comparing the clinical characteristics of people with CAPA to people without CAPA. The systematic review included cohort studies that investigated the clinical characteristics and outcomes of people who are hospitalised with proven or probable CAPA and confirmed COVID-19 (Bartoletti 2020; Delliere 2021; Gangneux 2020; Lahmer 2021; Segrelles-Calvo 2021; Van Biesen 2021; Velez Pintado 2021; Wang 2020).

The second study identified in this review (Prattes 2021) was a multinational cohort study that evaluated the risk factors associated with developing CAPA in people hospitalised and admitted to the intensive care for COVID-19 acute respiratory failure.

**Publication status**

The two studies included in this review were full publications (Chong 2021 and Prattes 2021). All 8 of the studies included in the systematic review (Chong 2021) were full publications as well.

**Study characteristics**

The Chong 2021 systematic review included 8 cohort studies, with 729 participants and ages ranging from 59-71 years. It included people who developed COVID-19 and were admitted to hospitals and later diagnosed with CAPA. The included studies collected data from participants during the early surges of COVID-19 in March-August 2020.

Prattes 2021 evaluated 592 participants, with 109/592 with proven, probable or possible CAPA who were admitted to ICU for COVID-19 acute respiratory failure. Participants in Prattes 2021 were aged between 54-75 years and were admitted between March 2020 – April 2021.

Both studies compared the clinical characteristics, or risk factors, of people with COVID-19 and confirmed CAPA with those without CAPA. The majority of participants in both studies were male (Chong 2021- 71.5% male and Prattes 2021 - 70.8% male), and were adults who were hospitalised with confirmed COVID-19. Participants were diagnosed with CAPA as defined by the ECMM criteria and the AspICU algorithm criteria.

For further details see the evidence review for risk factors of CAPA.

**What are the main results?**

The results from the studies indicated that there is a possible association between CAPA incidence and increasing

age, long-term corticosteroid treatment, higher sequential organ failure assessment (SOFA) score, progression to invasive mechanical ventilation and COVID-19 treatment with tocilizumab. There is an association of borderline significance between the presence of underlying chronic obstructive pulmonary disease (COPD) and CAPA.

**Our confidence in the results**

The certainty of the evidence for these risk factors was rated as low to very low, due to serious risk of bias with the studies controlling variables, due to serious indirectness (Prattes 2021) from the inclusion of people with possible CAPA (not proven or probable) and due to serious inconsistency as Chong 2021 analysed studies that varied methodologically.

The risk factors in the systematic review and the single cohort study are reported in general terms and not in detail. Details on confounding variables, such as diagnostic criteria and treatment regimens were not clearly defined. It was also unclear how these different variables were controlled in both the CAPA and non-CAPA groups, and how they were accounted for throughout data collection and analysis.

As both studies evaluated people from different waves of the COVID-19 pandemic, it is possible that changes in practice (e.g. treatments for COVID-19 in different centres, different diagnostic criteria for CAPA) throughout the COVID-19 pandemic context (e.g. surges and recovery periods in COVID-19 waves, take-up of vaccinations), may affect the number of people who contracted COVID-19 and CAPA.

Currently, there is limited evidence that identifies the associations between patient characteristics and CAPA development in COVID-19 disease and the current evidence base is small.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** No CAPA | **Intervention** CAPA | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| Risk factor - Age per 5 years<br>9 Critical | Hazard Ratio 1.18 (CI 95% 1.08 — 1.28) Based on data from 592 patients in 1 studies. (Observational (non-randomized)) | | CI 95% | Low Due to serious risk of bias, Due to serious indirectness [1] | Increasing age is associated with developing CAPA in people hospitalised with COVID-19 |
| Risk factor - Sex (Female)<br>9 Critical | Hazard Ratio 0.68 (CI 95% 0.42 — 1.09) Based on data from 592 patients in 1 studies. | | CI 95% | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [2] | Sex is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Sex (Male)<br>9 Critical | Odds Ratio 0.82 (CI 95% 0.43 — 1.55) Based on data from 514 patients in 1 studies. (Observational (non-randomized)) | | CI 95% | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [3] | Sex is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Number of coexisting conditions<br>9 Critical | Hazard Ratio 0.92 (CI 95% 0.76 — 1.1) Based on data from 592 patients in 1 studies. | | CI 95% | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [4] | Increasing numbers of coexisting conditions are not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** No CAPA | **Intervention** CAPA | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| Risk factor - History of smoking<br>9 Critical | Hazard Ratio 1.36 (CI 95% 0.76 — 2.44) Based on data from 529 patients in 1 studies. | | CI 95% | Very low<br>Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [5] | Smoking is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Obesity<br>9 Critical | Hazard Ratio 0.89 (CI 95% 0.54 — 1.44) Based on data from 592 patients in 1 studies. | | CI 95% | Very low<br>Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [6] | Obsesity is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Diabetes<br>9 Critical | Odds Ratio 1.2 (CI 95% 0.71 — 2.01) Based on data from 506 patients in 1 studies. (Observational (non-randomized)) | | CI 95% | Very low<br>Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [7] | Diabetes is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Diabetes<br>9 Critical | Hazard Ratio 1.12 (CI 95% 0.73 — 1.73) Based on data from 529 patients in 1 studies. | | CI 95% | Very low<br>Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [8] | Diabetes is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Cancer<br>9 Critical | Odds Ratio 2.25 (CI 95% 0.68 — 5.07) Based on data from 332 patients in 1 studies. (Observational (non-randomized)) | | CI 95% | Very low<br>Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [9] | Cancer is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - COPD<br>9 Critical | Odds Ratio 2.75 (CI 95% 1 — 7.52) Based on data from 514 patients in 1 studies. (Observational (non-randomized)) | | CI 95% | Low<br>Due to serious risk of bias, Due to serious inconsistency [10] | COPD is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Active malignant disease<br>9 Critical | Hazard Ratio 1.56 (CI 95% 0.81 — 3) Based on data from 529 patients in 1 studies. | | CI 95% | Very low<br>Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [11] | Active malignant disease is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** No CAPA | **Intervention** CAPA | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| Risk factor - Cardiovascular disease<br>9 Critical | Hazard Ratio 1.2 (CI 95% 0.81 — 1.78) Based on data from 529 patients in 1 studies. | | CI 95% | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [12] | Cardiovascular disease is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Pulmonary disease<br>9 Critical | Hazard Ratio 1.42 (CI 95% 0.89 — 2.24) Based on data from 529 patients in 1 studies. | | CI 95% | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [13] | Pulmonary disease is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Solid organ transplantation<br>9 Critical | Hazard Ratio 2.2 (CI 95% 0.9 — 5.42) Based on data from 529 patients in 1 studies. | | CI 95% | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [14] | Solid organ transplantation is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Long term corticosteroid use<br>9 Critical | Odds Ratio 3.53 (CI 95% 1.16 — 10.69) Based on data from 250 patients in 1 studies. (Observational (non-randomized)) | | CI 95% | Low Due to serious risk of bias, Due to serious inconsistency [15] | Long-term corticosteroid is associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Long term immunosuppressant<br>9 Critical | Odds Ratio 1.87 (CI 95% 0.28 — 12.29) Based on data from 142 patients in 1 studies. (Observational (non-randomized)) | | CI 95% | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [16] | Long-term immunosuppressant use is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Non-invasive ventilation<br>9 Critical | Hazard Ratio 0.08 (CI 95% 0.02 — 0.33) Based on data from 529 patients in 1 studies. | | CI 95% | Low Due to serious risk of bias,, Due to serious indirectness [17] | Non-invasive ventilation is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Extracorporeal Membrane Oxygenation (ECMO)<br>9 Critical | Hazard Ratio 0.8 (CI 95% 0.37 — 1.7) Based on data from 529 patients in 1 studies. | | CI 95% | Low Due to serious risk of bias, Due to serious indirectness [18] | Extracorporeal Membrane Oxygenation (ECMO) is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** No CAPA | **Intervention** CAPA | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| Risk factor - Invasive mechanical ventilation<br>9 Critical | Hazard Ratio 2.53 (CI 95% 1.53 — 4.17) Based on data from 529 patients in 1 studies. | | CI 95% | Low Due to serious risk of bias, Due to serious indirectness [19] | Invasive mechanical ventilation is significantly associated with an increased risk of developing CAPA in people hospitalized with COVID-19. |
| Risk factor - Any invasive ventilation<br>9 Critical | Hazard Ratio 2.93 (CI 95% 1.6 — 5.35) Based on data from 529 patients in 1 studies. | | CI 95% | Low Due to serious risk of bias, Due to serious indirectness [20] | Invasive ventilation of any kind is associated with an increased risk of developing CAPA in people hospitalized with COVID-19. |
| Risk factor - COVID-19 treatment with tocilizumab<br>9 Critical | Odds Ratio 1.85 (CI 95% 0.88 — 3.89) Based on data from 514 patients in 1 studies. (Observational (non-randomized)) | | CI 95% | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [21] | Treatment with tocilizumab for COVID-19 is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - COVID-19 treatment tocilizumab<br>9 Critical | Hazard Ratio 2.34 (CI 95% 1.03 — 4.06) Based on data from 529 patients in 1 studies. | | CI 95% | Low Due to serious risk of bias, Due to serious indirectness [22] | Treatment with tocilizumab for COVID-19 is associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - COVID-19 treatment with corticosteroid<br>9 Critical | Odds Ratio 0.69 (CI 95% 0.19 — 2.58) Based on data from 510 patients in 1 studies. | | CI 95% | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [23] | Treatment with corticosteroids for COVID-19 is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - COVID-19 treatment with glucocorticoids<br>9 Critical | Hazard Ratio 1.01 (CI 95% 0.68 — 1.5) Based on data from 529 patients in 1 studies. | | CI 95% | Low Due to serious risk of bias, Due to serious imprecision [24] | Treatment of COVID-19 with glucocorticoids is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - COVID-19 treatment with antibiotic | Odds Ratio 0.88 (CI 95% 0.39 — 1.97) Based on data from 542 patients in 1 studies. (Observational (non-randomized)) | | CI 95% | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [25] | Treatment of COVID-19 with antibiotics is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** No CAPA | **Intervention** CAPA | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| 9 Critical | | | | | |
| Risk factor - COVID-19 treatment with hydroxychloroquine<br>9 Critical | Odds Ratio 0.43 (CI 95% 0.07 — 2.68) Based on data from 514 patients in 1 studies. | | CI 95% | Very low<br>Due to serious inconsistency, Due to serious risk of bias, Due to serious imprecision [26] | Treatment of COVID-19 with hydroxychloroquine is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - COVID-19 treatment with azithromycin<br>9 Critical | Hazard Ratio 0.63 (CI 95% 0.33 — 1.21) Based on data from 529 patients in 1 studies. | | CI 95% | Low<br>Due to serious risk of bias, Due to serious imprecision [27] | Treatment of COVID-19 with azithromycin is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Risk factor - Age<br>9 Critical | Based on data from: 729 patients in 1 studies. | 59.25 (Mean)<br>Difference: | 66.58 (Mean)<br>**MD 7.52 more** ( CI 95% 2.02 more — 13.03 more ) | Low<br>Due to serious risk of bias, Due to serious inconsistency, [28] | Increasing age is associated with developing CAPA in people hospitalised with COVID-19 |
| Risk factor - BMI<br>9 Critical | Based on data from: 729 patients in 1 studies. | 27.88 (Mean)<br>Difference: | 27.8 (Mean)<br>**MD 0.46 fewer** ( CI 95% -1.93 fewer — 1.02 more ) | Very low<br>Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [29] | Increasing BMI is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |
| Sequential Organ Failure Assessment (SOFA) score<br>9 Critical | | 7.27 (Mean)<br>Difference: | 9.37 (Mean)<br>**MD 2.57 higher** ( CI 95% 1.46 higher — 3.68 higher ) | Low<br>Due to serious risk of bias, Due to serious inconsistency [30] | Increasing SOFA score is associated with an increased risk of developing CAPA in people hospitalised with COVID-19. |

1. **Risk of Bias: serious.** Unclear how variables in the study were controlled. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**
2. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
3. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world,

lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
4. **Risk of Bias: serious.** Unclear how variables were controlled.. **Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line o fno effect.
5. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
6. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
7. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
8. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
9. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
10. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
11. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
12. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
13. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
14. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
15. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
16. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious.** Differences amongst the populations included within the study. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
17. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**
18. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**
19. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**
20. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA.

**Imprecision: no serious. Publication bias: no serious.**
21. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
22. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**
23. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious.** Differences amongst the populations included within the study. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
24. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
25. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: serious.** Differences amongst the populations included within the study. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
26. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
27. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
28. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
29. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
30. **Risk of Bias: serious.** Unclear how variables are controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

### References

131. Chong WH, Saha BK, Neu KP : Comparing the clinical characteristics and outcomes of COVID-19-associate pulmonary aspergillosis (CAPA): a systematic review and meta-analysis. Infection 2021; Pubmed Journal

132. Prattes J, Wauters J, Giacobbe DR, Salmanton-García J, Maertens J, Bourgeois M, et al. : Risk factors and outcome of pulmonary aspergillosis in critically ill coronavirus disease 2019 patients-a multinational observational study by the European Confederation of Medical Mycology. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2021; Pubmed Journal

## Clinical Question/ PICO

**Population:** Signs and symptoms of people hospitalised with COVID-19 and with CAPA
**Intervention:** NA
**Comparator:** NA

## Summary

There is very limited evidence on symptoms of invasive pulmonary aspergillosis (IPA) in people who have or, as part of their acute illness, have had confirmed COVID-19.

**What is the evidence informing this conclusion?**

Evidence comes from one small, retrospective cohort study aiming to determine the prevalence of IPA and risk factors for IPA in people admitted to ICU due to severe SARS-CoV-2 infection (Segrellos-Calvo 2021).

**Publication status**

The included study has been published and peer-reviewed.

**Study characteristics**

The included study had seven participants. Their ages ranged from 42 to 75. Two participants (29%) were female. All had PCR-confirmed COVID-19. They were diagnosed with IPA using bronchoalveolar lavage using an Aspergillus EIA assay. All participants had been admitted to respiratory ICU.

For further details see the evidence review for signs and symptoms of CAPA.

**What are the main results?**

**Critical outcomes**

Fever, dyspnoea and cough were the most common symptoms among the participants (affecting 100%, 86% and 86% respectively).

**Important outcomes**

All outcomes for this review were classified as critical outcomes

**Our confidence in the results**

The evidence is extremely sparse and the results could be due to chance. The study was at high risk of bias due to a lack of detail about how outcomes were measured. There could also be variation over time or between people assessing symptoms, potentially introducing bias.

Outcomes were also downgraded twice for imprecision, as the precision of the result was not reported and could not be calculated.

The symptoms reported are also associated with COVID-19, and therefore it is not possible to attribute the symptoms to COVID-19 associated pulmonary aspergillosis (CAPA) alone.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** NA | **Intervention** NA | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| Symptom: Fever<br>During ICU admission<br>9 Critical | Based on data from: 7 patients in 1 studies. [1] (Observational (non-randomized)) | 7/7 (100%) of participants with CAPA had fever. No comparator group. | | Very low<br>Due to serious risk of bias, Due to very serious imprecision [2] | The prevalence of fever in people diagnosed with CAPA is uncertain. |
| Symptom: Dyspnoea<br>During ICU admission<br>9 Critical | Based on data from: 7 patients in 1 studies. (Observational (non-randomized)) | 6/7 (86%) of participants with CAPA had dyspnoea. No comparator group. | | Very low<br>Due to serious risk of bias, Due to very serious imprecision [3] | The prevalence of dyspnoea in people diagnosed with CAPA is uncertain. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** NA | **Intervention** NA | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **Symptom: Cough** During ICU admission<br>9 Critical | Based on data from: 7 patients in 1 studies. (Observational (non-randomized)) | 6/7 (86%) of participants with CAPA had cough. No comparator group. | | **Very low** Due to serious risk of bias, Due to very serious imprecision [4] | The prevalence of cough in people diagnosed with CAPA is uncertain. |
| **Symptom: Malaise** During ICU admission<br>9 Critical | Based on data from: 7 patients in 1 studies. (Observational (non-randomized)) | 3/7 (43%) of participants with CAPA had malaise. No comparator group. | | **Very low** Due to serious risk of bias, Due to very serious imprecision [5] | The prevalence of malaise in people diagnosed with CAPA is uncertain. |
| **Symptom: Sputum** During ICU admission<br>9 Critical | Based on data from: 7 patients in 1 studies. (Observational (non-randomized)) | 1/7 (14%) of participants with CAPA had sputum. No comparator group. | | **Very low** Due to serious risk of bias, Due to very serious imprecision [6] | The prevalence of sputum in people diagnosed with CAPA is uncertain. |
| **Symptom: Diarrhoea** During ICU admission<br>9 Critical | Based on data from: 7 patients in 1 studies. (Observational (non-randomized)) | 1/7 (14%) of participants with CAPA had diarrhoea. No comparator group. | | **Very low** Due to serious risk of bias, Due to very serious imprecision [7] | The prevalence of diarrhoea in people diagnosed with CAPA is uncertain. |
| **Symptom: Headache** During ICU admission<br>9 Critical | Based on data from: 7 patients in 1 studies. (Observational (non-randomized)) | 1/7 (14%) of participants with CAPA had headache. No comparator group. | | **Very low** Due to serious risk of bias, Due to very serious imprecision [8] | The prevalence of headache in people diagnosed with CAPA is uncertain. |

1. Primary study **Supporting references:** [129],
2. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
3. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
4. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
5. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
6. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute

the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
7. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
8. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**

### References

129. Segrelles-Calvo G, Araújo GRS, Llopis-Pastor E : Prevalence of opportunistic invasive aspergillosis in COVID-19 patients with severe pneumonia. Mycoses 2021; Pubmed Journal

Not recommended

New

Do not do diagnostic tests for CAPA if there is low clinical suspicion of the condition.

## Evidence To Decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

The panel were presented with information from a taskforce report by Verweij et al. on diagnosing and managing CAPA that prevalence of CAPA in people being treated in ICU was between 0% and 33% (the average across included studies was 9.3%). They discussed that this prevalence included possible as well as probable and proven CAPA, and was therefore likely to be an overestimation. The panel agreed that in their experience, prevalence of CAPA is low, and so testing for CAPA should only take place if there is clinical suspicion of the condition.

The panel were also presented with evidence from 2 systematic reviews (Chong 2021 and Dimopoulos 2021) and 2 primary studies (Meawed 2021 and van Grootveld 2021). The panel discussed the most common types of diagnostic tests and also referred to the taskforce report by Verweij et al.

The evidence showed that a range of different diagnostic test types are conducted to confirm CAPA diagnosis. The panel agreed that some of the common tests for diagnosing CAPA, for example bronchoalveolar lavage (BAL), are invasive and so the risks of carrying out the test should be considered against the benefit of a potential diagnosis.

**Certainty of the Evidence**

It was not possible to apply GRADE to the outcomes in this review, because the outcomes were descriptive rather than analytical.

The panel agreed that the studies were at moderate to high risk of bias due to high heterogeneity between study participants and variations in practice between study centres. The panel also agreed that the taskforce document was an up to date and relevant source of information on the diagnosis and treatment of CAPA. However, the panel also acknowledged that the evidence identified by the taskforce was sparse.

Based on this evidence the panel agreed that it would not be possible to determine the best diagnostic tests to request when CAPA was suspected. The panel agreed that unless CAPA was suspected clinically, further investigations for CAPA should not be carried out.

**Preference and values**

Substantial variability is expected or uncertain

The panel considered that some of the diagnostic tests for CAPA, for example a bronchoscopy or BAL, may involve clinical risk or patient discomfort and some people may be apprehensive about having it done. Therefore these tests should be carried out following an appropriate multidisciplinary discussion and decision on the clinical suspicion of CAPA.

The panel were not aware of any systematically collected data on preferences and values of people in relation to bronchoalveolar lavage sampling.

**Resources**

Important issues, or potential issues not investigated

This recommendation advises against investigation when suspicion is low, so has potential for savings in resource use from unnecessary procedures. Cost-effectiveness was not assessed as part of this evidence review.

**Equity**

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that investigations should take place in the same way for all people who are critically ill because of current or previous COVID-19.

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 the acceptability of assessing for suspicion of CAPA.

**Feasibility**

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about feasibility. They agreed that testing for CAPA only in cases where there is a clinical suspicion of CAPA should be feasible, especially where it results in a reduction in testing.

### Rationale

Because the incidence of CAPA is low, there is a lack of evidence on how to diagnose the condition. Also, there are no specific combinations of signs and symptoms for diagnosing it. The panel concluded that the likelihood of CAPA should be considered when deciding whether to do diagnostic tests.

## Clinical Question/ PICO

**Population:** Diagnostics for CAPA
**Intervention:** NA
**Comparator:** NA

### Summary

This review aimed to determine the diagnostic tests that should be used to diagnose CAPA in people with COVID-19. The evidence highlighted the range of tests that are used in clinical practice.

**What is the evidence informing this conclusion?**

Evidence comes from 2 systematic reviews that evaluate different diagnostic investigations for people with COVID-19 and suspected CAPA (Chong 2021 and Dimopoulos 2021). A further 2 studies were included in this

evidence review to supplement the findings of the included systematic reviews: a cross-sectional study (Meawed 2021) and a cohort study (van Grootveld 2021).

**Publication status**

All included studies were full publications (Chong 2021, Dimopoulos 2021, Meawed 2021 and van Grootveld 2021).

**Study characteristics**

Study participant numbers ranged from 63 people (van Grootveld 2021) to 1494 people (Chong 2021b). The average age of participants ranged from 62 to 63 years. The proportion of male participants ranged from 34% to 80% of the study population. All participants had a wide range of underlying comorbidities (for example, hypertension, diabetes, chronic pulmonary disease, cardiovascular disease, and active malignancies).

Most participants (94%; n= 2829/3026) were hospitalised and admitted to ICU with severe COVID-19 and only 6% had moderate COVID-19 (197/3026). Disease severity was mostly scored against the WHO Clinical Progression Scale.

For further details see the evidence review for diagnostics for CAPA.

**What are the main results?**

The evidence described the use of bronchoalveolar lavage (BAL), endotracheal aspirates (ETA), serum, non-directed bronchial lavage (NBL) and sputum to diagnose CAPA. The different microbiological investigations performed on each sample (such as tissue culture, galactomannan and beta-d-glucan biomarker levels, PCR) were also described in the literature.

CT imaging, serum assays (galactomannan (GM) and beta-d-glucan (BDG)), ETA culture and BAL are commonly used to support CAPA diagnosis. Further BAL sample investigations such as microscopy, culture, GM, BDG and PCR are also commonly used to support CAPA diagnosis.

The evidence shows that sputum sampling, NBL and ETA investigations like GM, BDG and PCR are not as commonly used to diagnose CAPA, as their prevalence was relatively low when compared to that of CT imaging, BAL, and serum assays.

The findings of this review are consistent with existing recommendations on diagnosing CAPA (Verweij et al. 2021). The Verweij et al. 2021 report states that bronchoscopy alongside BAL is recommended to diagnose CAPA and states that ETA and sputum should not be relied on solely to diagnose CAPA.

**Our confidence in the results**

GRADE could not be conducted on the results of this review because the results were descriptive rather than analytical.

There were some concerns about risk of bias due to unclear reporting of participant eligibility criteria in all studies (Chong 2021b, Dimopoulous 2021, Meawed 2021 and van Grootveld 2021). There was also insufficient information to assess the data collection and data analysis methods used in Chong 2021b and Dimopoulous 2021 and as such, risk of bias was rated as high for both studies.

The two systematic reviews contained studies from international centres and as such, there may have been differences in standard of care as well as diagnostic investigations and assessment criteria. As such, there is risk of the evidence being indirect to the UK context.

Although Chong 2021b defined clear eligibility criteria to limit the heterogeneity, studies are heterogeneous with epidemiological, clinical, and methodological diversity, meaning that it may not be possible to generalise the prevalence results.

**Conclusion**

The review has found that CT imaging, serum assays of biomarkers, ETA culture and BAL are the most common investigations for diagnosing CAPA.

The findings of this review are consistent with current recommendations on diagnosing CAPA.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** | **Intervention** | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| CT Imaging | Based on data from: 1,792 patients in 3 studies. | Three studies (n=1792) found that 10%- 43% of participants had undergone a CT imaging investigation to support CAPA diagnosis. | | | Evidence from four studies found that CT imaging is a common investigation used to support CAPA diagnosis. |
| Serum Galactomannan | Based on data from: 957 patients in 2 studies. | Two studies (n=957) found that 25%-47% of participants had undergone a serum galactomannan investigation to support CAPA diagnosis. | | | Evidence from two studies found that serum galactomannan is a common investigation used to support CAPA diagnosis. |
| Serum beta-D-glucan | Based on data from: 636 patients in 2 studies. | Two studies (n= 636) found that 3% - 47% of participants had undergone a serum beta-d-glucan investigation to support CAPA diagnosis. | | | Evidence from two studies found that serum beta-d-glucan is a common investigation used to support CAPA diagnosis. |
| Endotracheal Aspirate Culture | Based on data from: 370 patients in 3 studies. | Three studies (n = 370) found that 8% - 100% of a participants had undergone a endotracheal aspirate microscopy investigation to support CAPA diagnosis. | | | Evidence from three studies found that endotracheal aspirate culture is a common investigation used to support CAPA diagnosis |
| Endotracheal Aspirate Beta-d-glucan | Based on data from: 52 patients in 2 studies. | Two studies (n = 52) found that 4%-5% of participants had undergone a endotracheal aspirate beta-d-glucan investigation to support CAPA diagnosis. | | | Evidence from two studies found that endotracheal aspirate culture is not commonly used to support CAPA diagnosis. |
| Endotracheal Aspirate PCR | Based on data from: 63 patients in 1 studies. | One study (n = 63) found that 100% of patients had undergone a endotracheal aspirate PCR investigation to support CAPA diagnosis. | | | Evidence from one study found that endotracheal aspirate PCR is not commonly used to support CAPA diagnosis |
| Non-directed Bronchial Lavage Culture | Based on data from: 217 patients in 2 studies. | Two studies (n = 217) found that 5% - 10% of participants had undergone a non-directed bronchial lavage culture investigation to support CAPA diagnosis. | | | Evidence from two studies found that non-directed bronchial lavage culture is not commonly used to support CAPA diagnosis |
| Non-directed Bronchial Lavage Galactomannan | Based on data from: 78 patients in 2 studies. | Two studies (n=78) found that 1%-4% of participants had undergone a non-directed bronchial lavage galactomannan investigation to support CAPA diagnosis. | | | Evidence from two studies found that non-directed bronchial lavage galactomannan is not commonly used to |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** | **Intervention** | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| | | | | | support CAPA diagnosis |
| Non-directed Bronchial Lavage PCR | Based on data from: 66 patients in 2 studies. | Two studies (n=66) found that 1%-4% of participants had undergone a non-directed bronchial lavage PCR investigation to support CAPA diagnosis. | | | Evidence from two studies found that non-directed bronchial lavage PCR is not commonly used to support CAPA diagnosis |
| Bronchoalveolar Lavage Microscopy | Based on data from: 16 patients in 1 studies. | One study (n=16) found tha1% of participants had undergone a bronchoalveolar lavage microscopy investigation to support CAPA diagnosis. | | | Evidence from one study found that bronchoalveolar lavage microscopy is not commonly used to support CAPA diagnosis |
| Bronchoalveolar Lavage Culture | Based on data from: 572 patients in 3 studies. | Three studies (n = 572) found that 17% -22% of participants had undergone a bronchoalveolar lavage culture investigation to support CAPA diagnosis. | | | Evidence from three studies found that bronchoalveolar lavage culture is a common investigation to support CAPA diagnosis |
| Bronchoalveolar Lavage Galactomannan | Based on data from: 518 patients in 3 studies. | Three studies (n=518) found that 17%-30% of participants had undergone a bronchoalveolar lavage galactomannan investigation to support CAPA diagnosis. | | | Evidence from one study found that bronchoalveolar lavage galactomannan is a common investigation used to support CAPA diagnosis |
| Bronchoalveolar Lavage PCR | Based on data from: 540 patients in 4 studies. | Four studies (n=540) found that 4%-24% of participants had undergone a bronchoalveolar lavage PCR investigation to support CAPA diagnosis. | | | Evidence from four studies found that bronchoalveolar lavage PCR is a common investigation to support CAPA diagnosis |
| Sputum | Based on data from: 241 patients in 3 studies. | Three studies (n=241) found that 1%-100% of participants had undergone a sputum investigation to support CAPA diagnosis. | | | Evidence from three studies found that sputum sampling is not commonly used to support CAPA diagnosis |

## References

148. Chong WH, Neu KP : Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. The Journal of hospital infection 2021;113 115-129 Pubmed Journal

149. Dimopoulos G, Almyroudi M-P, Myrianthefs P, Rello J : COVID-19-Associated Pulmonary Aspergillosis (CAPA). Journal of Intensive Medicine 2021; Journal Website

151. van Grootveld R, van Paassen J, de Boer MGJ, Claas ECJ, Kuijper EJ, van der Beek MT : Systematic screening for COVID-19 associated invasive aspergillosis in ICU patients by culture and PCR on tracheal aspirate. Mycoses 2021;64(6):641-650 Pubmed Journal

Recommended

New

When investigating suspected CAPA:

- use a range of tests to increase the likelihood of making a confident diagnosis
- if possible, include bronchoalveolar lavage (BAL) as part of diagnostic testing, taking into account the risks of BAL in relation to the person's clinical condition
- discuss the diagnostic testing strategy and final diagnosis with a multidisciplinary team that includes infection specialists.

## Evidence To Decision

### Benefits and harms

Small net benefit, or little difference between alternatives

The panel were presented with evidence from 2 systematic reviews (Chong 2021 and Dimopoulos 2021), and 2 primary studies (Meawed 2021 and van Grootveld 2021). The panel also considered a taskforce report by Verweij et al. on diagnosing and managing CAPA.

The evidence described the frequency of diagnostic tests that are used to investigate CAPA. It showed that bronchoalveolar lavage (BAL) is one of the most commonly used diagnostic tests for diagnosing CAPA. Of the studies included, 55% of people had a BAL carried out, with further investigations on the sample (for example culture, galactomannan and PCR). The panel noted that BAL is carried out in intensive care units in people who are critically ill and invasively mechanically ventilated to investigate infectious lung disease.

The taskforce report discussed by the panel, recommends bronchoscopy with BAL, stating that it is the most important tool to diagnose invasive pulmonary aspergillosis, including in people who are critically ill and have, or have had, COVID-19 as part of their acute illness. The panel acknowledged that BAL is an invasive procedure that is not risk-free and may not be feasible to carry out in all patients, particularly in patients who remain on non-invasive ventilation.

The reviewed studies and the taskforce report also reported that other tests such as endotracheal aspirates, serological assays for beta-D-glucan and galactomannan (fungal biomarkers) are used to diagnose CAPA. Overall, the panel agreed that there are variations in the sensitivity and specificity of diagnostic tests, but that BAL may perform most favourably for the diagnosis of CAPA.

The panel concluded that BAL is the preferred diagnostic approach for investigating a CAPA diagnosis, but the risks and harms from carrying out the procedure need to be carefully assessed and other tests should be used alongside BAL or if BAL is not possible.

The panel discussed that, in their experience, a diagnosis of CAPA should usually be made as part of a multidisciplinary team with input from infection specialists, for example medical microbiologists or infectious disease specialists.

The panel agreed that the approach for diagnosing CAPA in children and young people should be the same as the approach for adults, however the levels of serum biomarkers may be different.

### Certainty of the Evidence

It was not possible to apply GRADE to the outcomes in this review, because the outcomes were descriptive rather than analytical.

The panel agreed that the studies were at moderate to high risk of bias due to high heterogeneity between study participants and variations in local practice in study centres. The panel agreed that the evidence informing the taskforce report by Verweij et al.on diagnosing and managing CAPA was sparse.

Based on the evidence, the panel agreed that it was not possible to identify with certainty which tests, and in which order, should be used to diagnose CAPA. They agreed with the taskforce report that a BAL is likely to be the most accurate test for diagnosing CAPA based on the evidence of comparisons of diagnostic tests in IPA more broadly.

**Preference and values**

No substantial variability expected

The panel agreed that people may experience discomfort during a bronchoalveolar lavage (BAL), and some people may be apprehensive about having it done. They suggested that the risks and patient experience may be different if the person is already on invasive mechanical ventilation. The panel suggested that people's preferences and values should be considered as part of the shared-decision making process with the patients and their families

The panel were not aware of any systematically collected data on preferences and values of people in relation to the different investigations that are used to diagnose CAPA.

**Resources**

Important issues, or potential issues not investigated

The panel discussed the need for timely testing and diagnostics to investigate CAPA. Since BAL is a commonly used diagnostic test for the assessment of pulmonary aspergillosis, it is not expected that this recommendation will lead to significant changes in resource utilisation.

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

**Equity**

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill because of current or previous COVID-19.

No other equity issues were identified.

**Acceptability**

Important issues, or potential issues not investigated

The panel discussed that, in their experience, there are few issues with acceptance of BAL as a diagnostic tool for CAPA among people who are critically ill and have, or have had, COVID-19 as part of their acute illness. However, the panel noted that in some cases, people may reject BAL or bronchoscopy as it may cause some discomfort.

**Feasibility**

No important issues with the recommended alternative

The panel identified several potential barriers to feasibility for this recommendation. They noted that while BAL is recommended to diagnose CAPA, a wait is required for the results of BAL to become available. The panel noted that bronchoscopy may not always be feasible to carry out in patients with suspected CAPA. The panel addressed these feasibility concerns by ensuring that other diagnostic tests for CAPA were also included in the recommendation.

### Rationale

There is a lack of evidence on diagnosing CAPA, including on what diagnostic tests to use, how frequently to test and the diagnostic value of the different investigations. The panel noted that using a range of tests, including bronchoalveolar lavage (BAL), follows current best practice recommended in a taskforce report by Verweij et al., (2021) on diagnosing and managing CAPA.

Because BAL is an invasive procedure, it is important that any benefits or harms are considered before using it to investigate CAPA. The panel noted that BAL may not always be suitable or feasible. They agreed that other tests could be used instead of BAL, such as serological assays, non-bronchoscopic lavage or endotracheal aspirates.

## Clinical Question/ PICO

**Population:** Diagnostics for CAPA
**Intervention:** NA
**Comparator:** NA

### Summary

This review aimed to determine the diagnostic tests that should be used to diagnose CAPA in people with COVID-19. The evidence highlighted the range of tests that are used in clinical practice.

**What is the evidence informing this conclusion?**

Evidence comes from 2 systematic reviews that evaluate different diagnostic investigations for people with COVID-19 and suspected CAPA (Chong 2021 and Dimopoulos 2021). A further 2 studies were included in this evidence review to supplement the findings of the included systematic reviews: a cross-sectional study (Meawed 2021) and a cohort study (van Grootveld 2021).

**Publication status**

All included studies were full publications (Chong 2021, Dimopoulos 2021, Meawed 2021 and van Grootveld 2021).

**Study characteristics**

Study participant numbers ranged from 63 people (van Grootveld 2021) to 1494 people (Chong 2021b). The average age of participants ranged from 62 to 63 years. The proportion of male participants ranged from 34% to 80% of the study population. All participants had a wide range of underlying comorbidities (for example, hypertension, diabetes, chronic pulmonary disease, cardiovascular disease, and active malignancies).

Most participants (94%; n= 2829/3026) were hospitalised and admitted to ICU with severe COVID-19 and only 6% had moderate COVID-19 (197/3026). Disease severity was mostly scored against the WHO Clinical Progression Scale.

For further details see the evidence review for diagnostics for CAPA.

**What are the main results?**

The evidence described the use of bronchoalveolar lavage (BAL), endotracheal aspirates (ETA), serum, non-directed bronchial lavage (NBL) and sputum to diagnose CAPA. The different microbiological investigations performed on each sample (such as tissue culture, galactomannan and beta-d-glucan biomarker levels, PCR) were also described in the literature.

CT imaging, serum assays (galactomannan (GM) and beta-d-glucan (BDG)), ETA culture and BAL are commonly used to support CAPA diagnosis. Further BAL sample investigations such as microscopy, culture, GM, BDG and PCR are also commonly used to support CAPA diagnosis.

The evidence shows that sputum sampling, NBL and ETA investigations like GM, BDG and PCR are not as commonly used to diagnose CAPA, as their prevalence was relatively low when compared to that of CT imaging, BAL, and serum assays.

The findings of this review are consistent with existing recommendations on diagnosing CAPA (Verweij et al. 2021). The Verweij et al. 2021 report states that bronchoscopy alongside BAL is recommended to diagnose CAPA and states that ETA and sputum should not be relied on solely to diagnose CAPA.

**Our confidence in the results**

GRADE could not be conducted on the results of this review because the results were descriptive rather than analytical.

There were some concerns about risk of bias due to unclear reporting of participant eligibility criteria in all studies (Chong 2021b, Dimopoulous 2021, Meawed 2021 and van Grootveld 2021). There was also insufficient information to assess the data collection and data analysis methods used in Chong 2021b and Dimopoulous 2021 and as such, risk of bias was rated as high for both studies.

The two systematic reviews contained studies from international centres and as such, there may have been differences in standard of care as well as diagnostic investigations and assessment criteria. As such, there is risk of

the evidence being indirect to the UK context.

Although Chong 2021b defined clear eligibility criteria to limit the heterogeneity, studies are heterogeneous with epidemiological, clinical, and methodological diversity, meaning that it may not be possible to generalise the prevalence results.

**Conclusion**

The review has found that CT imaging, serum assays of biomarkers, ETA culture and BAL are the most common investigations for diagnosing CAPA.

The findings of this review are consistent with current recommendations on diagnosing CAPA.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** | **Intervention** | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| CT Imaging | Based on data from: 1,792 patients in 3 studies. | Three studies (n=1792) found that 10%- 43% of participants had undergone a CT imaging investigation to support CAPA diagnosis. | | | Evidence from four studies found that CT imaging is a common investigation used to support CAPA diagnosis. |
| Serum Galactomannan | Based on data from: 957 patients in 2 studies. | Two studies (n=957) found that 25%-47% of participants had undergone a serum galactomannan investigation to support CAPA diagnosis. | | | Evidence from two studies found that serum galactomannan is a common investigation used to support CAPA diagnosis. |
| Serum beta-D-glucan | Based on data from: 636 patients in 2 studies. | Two studies (n= 636) found that 3% - 47% of participants had undergone a serum beta-d-glucan investigation to support CAPA diagnosis. | | | Evidence from two studies found that serum beta-d-glucan is a common investigation used to support CAPA diagnosis. |
| Endotracheal Aspirate Culture | Based on data from: 370 patients in 3 studies. | Three studies (n = 370) found that 8% - 100% of a participants had undergone a endotracheal aspirate microscopy investigation to support CAPA diagnosis. | | | Evidence from three studies found that endotracheal aspirate culture is a common investigation used to support CAPA diagnosis |
| Endotracheal Aspirate Beta-d-glucan | Based on data from: 52 patients in 2 studies. | Two studies (n = 52) found that 4%-5% of participants had undergone a endotracheal aspirate beta-d-glucan investigation to support CAPA diagnosis. | | | Evidence from two studies found that endotracheal aspirate culture is not commonly used to support CAPA diagnosis. |
| Endotracheal Aspirate PCR | Based on data from: 63 patients in 1 studies. | One study (n = 63) found that 100% of patients had undergone a endotracheal aspirate PCR investigation to support CAPA diagnosis. | | | Evidence from one study found that endotracheal aspirate PCR is not commonly used to support CAPA |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** | **Intervention** | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| | | | | | diagnosis |
| Non-directed Bronchial Lavage Culture | Based on data from: 217 patients in 2 studies. | Two studies (n = 217) found that 5% - 10% of participants had undergone a non-directed bronchial lavage culture investigation to support CAPA diagnosis. | | | Evidence from two studies found that non-directed bronchial lavage culture is not commonly used to support CAPA diagnosis |
| Non-directed Bronchial Lavage Galactomannan | Based on data from: 78 patients in 2 studies. | Two studies (n=78) found that 1%-4% of participants had undergone a non-directed bronchial lavage galactomannan investigation to support CAPA diagnosis. | | | Evidence from two studies found that non-directed bronchial lavage galactomannan is not commonly used to support CAPA diagnosis |
| Non-directed Bronchial Lavage PCR | Based on data from: 66 patients in 2 studies. | Two studies (n=66) found that 1%-4% of participants had undergone a non-directed bronchial lavage PCR investigation to support CAPA diagnosis. | | | Evidence from two studies found that non-directed bronchial lavage PCR is not commonly used to support CAPA diagnosis |
| Bronchoalveolar Lavage Microscopy | Based on data from: 16 patients in 1 studies. | One study (n=16) found tha1% of participants had undergone a bronchoalveolar lavage microscopy investigation to support CAPA diagnosis. | | | Evidence from one study found that bronchoalveolar lavage microscopy is not commonly used to support CAPA diagnosis |
| Bronchoalveolar Lavage Culture | Based on data from: 572 patients in 3 studies. | Three studies (n = 572) found that 17% -22% of participants had undergone a bronchoalveolar lavage culture investigation to support CAPA diagnosis. | | | Evidence from three studies found that bronchoalveolar lavage culture is a common investigation to support CAPA diagnosis |
| Bronchoalveolar Lavage Galactomannan | Based on data from: 518 patients in 3 studies. | Three studies (n=518) found that 17%-30% of participants had undergone a bronchoalveolar lavage galactomannan investigation to support CAPA diagnosis. | | | Evidence from one study found that bronchoalveolar lavage galactomannan is a common investigation used to support CAPA diagnosis |
| Bronchoalveolar Lavage PCR | Based on data from: 540 patients in 4 studies. | Four studies (n=540) found that 4%-24% of participants had undergone a bronchoalveolar lavage PCR investigation to support CAPA diagnosis. | | | Evidence from four studies found that bronchoalveolar lavage PCR is a common investigation to support CAPA diagnosis |

| Outcome Timeframe | Study results and measurements | Comparator | Intervention | Certainty of the Evidence (Quality of evidence) | Plain language summary |
|---|---|---|---|---|---|
| Sputum | Based on data from: 241 patients in 3 studies. | Three studies (n=241) found that 1%-100% of participants had undergone a sputum investigation to support CAPA diagnosis. | | | Evidence from three studies found that sputum sampling is not commonly used to support CAPA diagnosis |

## References

148. Chong WH, Neu KP : Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. The Journal of hospital infection 2021;113 115-129 Pubmed Journal

149. Dimopoulos G, Almyroudi M-P, Myrianthefs P, Rello J : COVID-19-Associated Pulmonary Aspergillosis (CAPA). Journal of Intensive Medicine 2021; Journal Website

151. van Grootveld R, van Paassen J, de Boer MGJ, Claas ECJ, Kuijper EJ, van der Beek MT : Systematic screening for COVID-19 associated invasive aspergillosis in ICU patients by culture and PCR on tracheal aspirate. Mycoses 2021;64(6):641-650 Pubmed Journal

Consensus recommendation

New

Test for antifungal resistance if an Aspergillus isolate is cultured from a CAPA test sample.

## Evidence To Decision

### Benefits and harms

Small net benefit, or little difference between alternatives

The panel discussed the risks of antifungal resistance and agreed on the importance of testing for antifungal resistance to guide treatment decisions for CAPA. Resistance to azoles, a type of antifungal treatment, would affect the treatment options available and the panel therefore agreed that resistance should be tested for as soon as possible.

The panel understood that waiting for the results of antifungal resistance tests could lead to a delay in effective treatment. Therefore, the panel advised that CAPA treatment could be started based on clinical judgement while waiting for test results. However, the panel emphasised the importance of using the results of antifungal resistance testing to guide definitive treatment.

The panel was not aware of any harms posed to patients from testing for antifungal resistance, but agreed that there were strong benefits from carrying out antifungal resistance testing as it could aid in identifying the optimal treatment for a CAPA patient.

### Certainty of the Evidence

No evidence was identified on antifungal resistance testing and diagnostic investigations for CAPA. However, the panel highlighted the need for a recommendation and stated that despite the lack of evidence on antifungal resistance in CAPA, based on their experience and expertise, this recommendation should be made to guide clinical management and decision making.

**Preference and values**

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on preferences and values of people in relation to testing for antifungal resistance.

**Resources**

Important issues, or potential issues not investigated

The panel discussed the need for timely testing and diagnostics to investigate CAPA and agreed that testing was important to guide the need for further intervention, and any resource implications may be offset by savings from prompt treatment.

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

**Equity**

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill because of current or previous COVID-19.

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 the acceptability of testing for antifungal resistance.

**Feasibility**

No important issues with the recommended alternative

The panel discussed that testing for antifungal resistance may not be routine in all centres, and that feasibility will require access to laboratory expertise.

## Rationale

In clinical practice, microbiological investigations can be used to assess antifungal resistance of isolates cultured from test samples. The panel noted the importance of testing for azole resistance to support clinical management decisions and ensure that suitable antifungal treatments are used. They agreed that treatment can be started before test results are confirmed, but should be reviewed when test results are available.

See the British Society for Medical Mycology's guidance on therapeutic drug monitoring of antifungal agents.

Consensus recommendation

New

Commissioners and local trusts should ensure that results of diagnostic tests for CAPA are available in a timeframe that informs and supports clinical decision making.

## Evidence To Decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

The panel highlighted the benefits of tests results being available quickly. They agreed that this would more often allow treatment to be started only after a confirmed diagnosis, rather than either starting treatment before diagnosis or accepting delays to treatment. Timely test results would reduce the frequency of treatment being used where diagnosis of CAPA is later determined to be negative, supporting antifungal stewardship aims.

**Certainty of the Evidence**

The panel did not review any evidence related to the time to availability of diagnostic tests for CAPA but advised that a recommendation was needed on this topic to ensure improved standardisation across centres. The panel's recommendation was based on their experience observing the variability in arrangements for processing diagnostic tests for CAPA.

**Preference and values**

No substantial variability expected

The panel were not aware of any systematically collected data on preferences and values of people in relation to testing for CAPA.

**Resources**

Important issues, or potential issues not investigated

The panel discussed the need for timely testing and diagnostics to investigate CAPA. They were aware that this might require additional resources, or changes to current processes in some areas, but concluded that the impact would be offset by the savings from appropriate diagnosis and treatment for people with CAPA, which could result in fewer days in hospital and reduced mortality among people with CAPA.

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

**Equity**

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but agreed testing should take place in the same way for all people who are critically ill because of current or previous COVID-19.

No other equity issues were identified.

**Acceptability**

Important issues, or potential issues not investigated

The panel were not aware of any barriers to acceptability in ensuring test results for CAPA are available in a timeframe that supports clinical decision-making.

**Feasibility**

No important issues with the recommended alternative

The panel acknowledged that while some centres can already provide rapid turnaround of tests for CAPA, other centres may be required to make changes to practice to adhere to this recommendation, which may be challenging to implement. However, these changes will support improved care for people who are critically ill and have suspected CAPA.

## Rationale

The panel noted that results of laboratory tests, in particular fungal antigen tests, are needed to diagnose CAPA. They also noted that if test results are not timely, there could be a delay in treatment or people could have treatments that they do not need. They highlighted the importance of having test results available in an appropriate timeframe to support clinical decision making and to improve people's outcomes.

Consensus recommendation

New

Monitor and report testing for, and diagnosis and management of, CAPA in line with local protocols.

*Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.*

## Evidence To Decision

### Benefits and harms

Small net benefit, or little difference between alternatives

The panel discussed the fact that there is insufficient evidence around the prevalence and management of CAPA. The panel agreed that monitoring and reporting on CAPA in line with local protocols would therefore provide useful information which could be used to improve identification and management of people with CAPA in the future.

### Certainty of the Evidence

There was no evidence on the monitoring and reporting of diagnostics used for CAPA. As such, the panel highlighted the importance of monitoring and reporting the prevalence and management of CAPA.

### Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data about the preferences and values for monitoring and reporting testing, in people who are suspected to have CAPA.

### Resources

No important issues with the recommended alternative

The panel discussed the need for monitoring and reporting clinical management of CAPA. Although this could require additional resource demands, the panel concluded that the information being recorded could inform and improve future testing, diagnosis, and management of CAPA through better understanding of when to test and treat.

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

### Equity

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill because of current or previous COVID-19.

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 the acceptability of monitoring and reporting for CAPA.

### Feasibility

No important issues with the recommended alternative

The panel acknowledged that while some centres already have processes in place to support reporting of CAPA testing,

diagnosis, and management, other centres may be required to make changes to practice in order to adhere to this recommendation, which may be challenging to implement. However, these changes could support continuous improvement of care.

### Rationale

There is a lack of evidence on the tests used to diagnose CAPA and on treatments for CAPA in people who are critically ill and have, or have had, COVID-19 as part of their acute illness. So, the panel agreed that local protocols should be developed to collect more information on the current prevalence of CAPA and practices for diagnosing and managing the condition.

## 9.2.2 Treating CAPA

Consensus recommendation

New

Only use antifungal treatments to treat CAPA if:

- diagnostic investigations support a diagnosis of CAPA or
- the results of diagnostic investigations are not available yet, but CAPA is suspected, and a multidisciplinary team or local protocols support starting treatment.

*See NICE's recommendations on diagnosing CAPA.*

### Evidence To Decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

The panel considered that there are risks from inappropriate use of antifungal agents, including antifungal resistance and adverse drug effects. The panel concluded that the harms of antifungal therapies used for CAPA outweigh the benefits in people who do not have evidence of invasive pulmonary aspergillosis. The panel agreed that antifungal treatments for CAPA should not be offered unless CAPA has been diagnosed or there is clinical suspicion of CAPA and a local multidisciplinary team including infection specialists (for example, medical microbiologists or infectious disease specialists) support starting treatment.

**Certainty of the Evidence**

The panel reviewed evidence on the effectiveness of treatments for people with CAPA. A review of the evidence only found one study available that directly investigates the effect of a specific treatment for patients with CAPA, and the panel agreed that the certainty of the evidence was very low. The study did not present evidence on when antifungal treatments for CAPA should be started.

The panel decision was based on their experience and prior knowledge of the clinical use of antifungal agents and when treatment with these agents should be started. They also drew on expertise about antifungal resistance when making this recommendation.

**Preference and values**

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on people's preferences and values.

The panel agreed that it was likely that people would not want to take a treatment with no known benefits but well-established side effects in situations when there is a low suspicion of CAPA.

**Resources**

Important issues, or potential issues not investigated

No formal analysis of resource impact has been carried out. However, it is possible that this recommendation will result in a reduction in the use of antifungals when there is low clinical suspicion or before investigations take place.

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

**Equity**

Important issues, or potential issues not investigated

This recommendation is not expected to cause inequity in any subgroups. Since CAPA is most likely to affect those with the most severe COVID-19 infections, the panel noted that subgroups with disproportionately high incidence of severe COVID-19 infection may be most affected by CAPA.

The panel recognised that the effectiveness and safety of antifungals may differ in pregnant women and children but that there was no evidence in this area.

No other equity issues were identified.

**Acceptability**

Important issues, or potential issues not investigated

While there was no systematically collected evidence about acceptability, the panel acknowledged that not giving antifungal treatment until CAPA is diagnosed or testing is underway may mean treatment is started later, or not at all, for some people. They acknowledged that clinicians treating people who are hospitalised with COVID-19 will seek to improve people's health outcomes as much as possible, and that families and carers of people who are hospitalised with COVID-19 would be likely to want to ensure that appropriate measures are taken to support people.

**Feasibility**

No important issues with the recommended alternative

This recommendation may reflect usual practice in some centres. For others it may require adjustments to practice which should be feasible to implement, as this recommendation seeks to ensure appropriate practice and potentially reduce over prescribing.

## Rationale

The panel noted that there are risks with antifungal treatments for CAPA, including antifungal resistance and adverse effects. They agreed that treatment should only be started if investigations support a diagnosis of CAPA, or a multidisciplinary team agrees to start treatment.

## Clinical Question/ PICO

**Population:** People hospitalised with COVID-19 and with CAPA
**Intervention:** Voriconazole
**Comparator:** Other

### Summary

**What is the evidence informing this conclusion?**

Evidence comes from one cohort study (Bartoletti 2020) that compared the survival outcomes of people hospitalised with COVID-19 and CAPA, who had, or did not have, treatment with voriconazole.

**Publication status**

The study referenced in this review was a full publication that had been peer-reviewed.

**Study characteristics**

Bartoletti 2020 was a prospective, multicentre cohort study that aimed to describe the incidence and outcomes of

CAPA in a larger cohort of people hospitalised with COVID-19 and receiving mechanical ventilation. A total of 108 people with COVID-19 that were treated in hospitals in Bologna, Italy, between February and March 2020 were screened for CAPA using bronchoalveolar lavage (BAL). Of these, 30 people were identified as having COVID-19 and CAPA.

For further details see the evidence review for treatments for CAPA.

**What are the main results?**

Of the 30 people who were identified as having COVID-19 and CAPA, 13 were treated with voriconazole, an antifungal therapy. Another 3 patients were treated with a different antifungal therapy, and the study authors do not state what treatment the remaining 14 patients received. Survival at 10, 20, and 30 days after ICU admission was captured for the 30 people with COVID-19 and CAPA, and differences were noted between the group of patients that were treated with voriconazole (n=13) vs. those not treated with voriconazole (n=17). At the end of the 30 days, 7 patients were still alive in each group.

**Our confidence in the results**

The certainty of the evidence for differences in survival between voriconazole treated CAPA patients vs. CAPA patients not treated with voriconazole was rated as very low, due to the small sample size, serious risk of confounding and imprecision.

The study found that there was no statistically significant difference in survival between CAPA patients treated with voriconazole compared with those not treated with voriconazole at 10, 20, and 30 days after ICU admission. However, the study was not powered to detect a difference for this outcome.

Study authors do not provide baseline characteristics for patients by treatment group, nor do they explain the methods used to assign patients to treatment groups. Since it is unclear if the patients treated with voriconazole are different from patients not treated with voriconazole with regards to characteristics that might impact their survival, there is a serious risk of confounding.

**Conclusion**

There was low quality evidence from one cohort study (Bartoletti 2020) reporting on possible treatments for CAPA.

The study showed that, in people with COVID-19 and CAPA, there were no statistically significant differences in survival for those treated with voriconazole compared with those not treated with voriconazole, at 10, 20, and 30 days from ICU admission.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Other | **Intervention** Voriconazole | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **10-Day Survival**<br>9 Critical | Relative risk 1.43 (CI 95% 0.97 — 2.1) Based on data from 30 patients in 1 studies. [1] (Observational (non-randomized)) | 647 per 1000<br>Difference: | 925 per 1000<br>**278 more per 1000** ( CI 95% 19 fewer — 712 more ) | **Very low** Due to very serious risk of bias and very serious imprecision [2] | One study found no statistically significant difference in 10- day survival in people having voriconazole compared with people not having voriconazole |
| **20-Day Survival**<br>9 Critical | Relative risk 1.05 (CI 95% 0.58 — 1.88) Based on data from 30 patients in 1 studies. [3] (Observational (non-randomized)) | 588 per 1000<br>Difference: | 617 per 1000<br>**29 more per 1000** ( CI 95% 247 fewer — 517 more ) | **Very low** Due to very serious risk of bias and very serious imprecision [4] | One study found no statistically significant difference in 20- day survival in people having voriconazole compared with people not having voriconazole |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Other | **Intervention** Voriconazole | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **30-Day Survival**<br><br>9 Critical | Relative risk 1.31 (CI 95% 0.61 — 2.79) Based on data from 30 patients in 1 studies. [5] | 412 per 1000<br><br>Difference: | 540 per 1000<br><br>**128 more per 1000** ( CI 95% 161 fewer — 737 more ) | **Very low** Due to very serious risk of bias and very serious imprecision [6] | One study found no statistically significant difference in 30- day survival in people having voriconazole compared with people not having voriconazole |

1. Systematic review [145] with included studies: Bartoletti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the 'other' therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 10-day survival between patients treated with voriconazole vs. other therapies.. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome.. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.
3. Systematic review [145] with included studies: Bartoletti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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### References

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145. Voriconazole versus [not] for CAPA.

Recommended

New

When considering antifungal treatment for CAPA:

- discuss treatment options with a multidisciplinary team that includes infection specialists
- follow local protocols that include best practice guidance on treating invasive aspergillosis.

*There is not enough evidence to recommend specific antifungal treatments for CAPA.*

*The panel noted the importance of national antifungal stewardship guidance, such as NICE's guideline on antimicrobial stewardship.*

## Evidence To Decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

The panel agreed that there is not enough evidence to recommend specific treatments for people with CAPA. Currently there is only one study available that directly investigates the effect of a specific treatment for patients with CAPA. This study (Bartoletti 2021) shows no statistically significant effect of voriconazole on the survival of people with CAPA. The panel noted that this was a small study with 30 participants, and that it provided limited insights on the benefits or harms of voriconazole. No safety outcomes are explored in this study. Based on this information, the panel recommended that decisions around treatments for people with CAPA be discussed with a multidisciplinary team that includes infection specialists, for example medical microbiologists or infectious disease specialists. Decisions around treatments for CAPA should also align with local protocols that include guidance on treating invasive aspergillosis.

The panel acknowledged that in many cases, antifungal therapies may be considered for the management of CAPA. They discussed the risks of antifungal resistance and agreed that the national antifungal stewardship strategy should be consulted if antifungal therapies are being considered for CAPA.

See the NICE's guideline on antimicrobial stewardship for more on the risks from antifungal resistance and recommendations for best practice.

**Certainty of the Evidence**

Very low

The overall certainty of the evidence for treatments for CAPA is very low.

Currently there is only one study available that directly investigates the effect of a specific treatment for patients with CAPA. In this non-randomised study (Bartoletti 2021), 30 people hospitalised with CAPA were treated either with voriconazole or another treatment, based on clinician discretion. The control group had either no treatment, or another

unspecified antifungal.

The panel reviewed this study and found that there is significant risk of bias in the results due to lack of randomisation, and significant imprecision due to the small study size. Additionally, there is a lack of clarity around the comparators used in this study. Evidence did not include young people and children, therefore it was not possible for the panel to discuss differences that might be required between adults and young people

Ultimately, the panel agreed that there is not enough evidence to recommend voriconazole or any other specific antifungal treatment for managing CAPA.

**Preference and values**

No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences about treatments for CAPA. They discussed that, in view of the lack of clear evidence about the treatments, most people would prefer for treatment decisions to be made based on best practice and relevant expertise.

**Resources**

Important issues, or potential issues not investigated

Cost effectiveness was not assessed as part of the evidence review and no formal analysis of resource impact has been carried out. The panel recommended further research on cost-effectiveness of CAPA treatment as part of the research recommendations.

**Equity**

Important issues, or potential issues not investigated

This recommendation is not expected to cause inequity among any subgroups. Since CAPA is most likely to affect those with the most severe COVID-19 infections, the panel noted that subgroups with disproportionately high incidence of severe COVID-19 infection may be most affected by CAPA

The panel recognised that the effectiveness and safety of antifungals may differ in pregnant women and children, but that there was no evidence in this area.

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. Since this recommendation does not recommend a specific treatment and instead defers to best practice and relevant expertise, it is not expected that there are significant barriers to acceptability. There may be variation in existing practice that the development of local protocols will need to resolve.

The panel acknowledged that some clinicians may feel that voriconazole should be recommended for treatment of CAPA. However, the panel agreed that there is not enough evidence to support the use of voriconazole, and decisions should be taken after discussing with multidisciplinary team.

**Feasibility**

No important issues with the recommended alternative

This recommendation refers to local protocols and decision-making as part of a multidisciplinary team, and therefore should be feasible to implement.

### Rationale

The panel noted the lack of evidence on treatments for CAPA. They agreed that treatment decisions, including on when to start treatment, should be guided by advice from infection specialists, and in line with local protocols and best practice guidelines.

For information on monitoring antifungal treatments, see the British Society for Medical Mycology's guidance on therapeutic drug monitoring of antifungal agents.

## Clinical Question/ PICO

**Population:** People hospitalised with COVID-19 and with CAPA
**Intervention:** Voriconazole
**Comparator:** Other

### Summary

**What is the evidence informing this conclusion?**

Evidence comes from one cohort study (Bartoletti 2020) that compared the survival outcomes of people hospitalised with COVID-19 and CAPA, who had, or did not have, treatment with voriconazole.

**Publication status**

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**Study characteristics**

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For further details see the evidence review for treatments for CAPA.

**What are the main results?**

Of the 30 people who were identified as having COVID-19 and CAPA, 13 were treated with voriconazole, an antifungal therapy. Another 3 patients were treated with a different antifungal therapy, and the study authors do not state what treatment the remaining 14 patients received. Survival at 10, 20, and 30 days after ICU admission was captured for the 30 people with COVID-19 and CAPA, and differences were noted between the group of patients that were treated with voriconazole (n=13) vs. those not treated with voriconazole (n=17). At the end of the 30 days, 7 patients were still alive in each group.

**Our confidence in the results**

The certainty of the evidence for differences in survival between voriconazole treated CAPA patients vs. CAPA patients not treated with voriconazole was rated as very low, due to the small sample size, serious risk of confounding and imprecision.

The study found that there was no statistically significant difference in survival between CAPA patients treated with voriconazole compared with those not treated with voriconazole at 10, 20, and 30 days after ICU admission. However, the study was not powered to detect a difference for this outcome.

Study authors do not provide baseline characteristics for patients by treatment group, nor do they explain the methods used to assign patients to treatment groups. Since it is unclear if the patients treated with voriconazole are different from patients not treated with voriconazole with regards to characteristics that might impact their survival, there is a serious risk of confounding.

**Conclusion**

There was low quality evidence from one cohort study (Bartoletti 2020) reporting on possible treatments for CAPA.

The study showed that, in people with COVID-19 and CAPA, there were no statistically significant differences in survival for those treated with voriconazole compared with those not treated with voriconazole, at 10, 20, and 30 days from ICU admission.

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### References

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145. Voriconazole versus [not] for CAPA.

Consensus recommendation

New

For people having antifungal treatment for suspected CAPA, stop treatment if the results of investigations do not support a diagnosis of CAPA and a multidisciplinary team agrees.

## Evidence To Decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

The panel noted that, on occasion, people will start antifungal treatments for CAPA while a diagnosis of CAPA is being confirmed. The panel agreed that antifungal treatments should usually be stopped if subsequent test results do not support a diagnosis of CAPA.

However, the panel also acknowledged that the performance of diagnostic tests for CAPA is variable and may be influenced by the clinical context. Therefore, the panel recommended that, in cases where treatment has been started before a diagnosis of CAPA is confirmed, a multidisciplinary team including infection specialists (for example, medical microbiologists or infectious disease specialists) should review test results. Where tests do not support a diagnosis of CAPA, consider stopping antifungal treatment.

**Certainty of the Evidence**

The panel decision was based on their experience and prior knowledge of the patient harms of antifungal treatments and national antimicrobial resistance strategies. The panel were not aware of any studies directly investigating the patient harms and risks of antifungal resistance from the use of antifungals for the treatment of CAPA.

**Preference and values**

No substantial variability expected

The panel were not aware of any systematically collected data on people's preferences and values.

The panel agreed that it was likely that people would not want to continue taking a treatment with no known benefits but well-established side effects where diagnostic testing does not support a diagnosis of CAPA.

**Resources**

Important issues, or potential issues not investigated

No formal analysis of resource impact has been carried out. However, it is possible that this recommendation will result in a shorter course of antifungals for some people.

Cost effectiveness was not assessed as part of the evidence review, but the panel recommended further research on this topic.

**Equity**

Important issues, or potential issues not investigated

This recommendation is not expected to cause inequity in any subgroups. Since CAPA is most likely to affect those with the most severe COVID-19 infections, the panel noted that subgroups with disproportionately high incidence of severe COVID-19 infection may be most affected by CAPA.

**Acceptability**

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about acceptability of stopping treatment for CAPA. It is likely that stopping treatment where results of investigations do not support a diagnosis of CAPA will be acceptable to most people when considering the recognised risk of adverse drug effects and the important antifungal stewardship implications.

**Feasibility**

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about feasibility. This recommendation aims to reduce variation, so there may be a need for a change in practice in some centres.

### Rationale

The panel noted the importance of good antifungal stewardship for reducing the risk of adverse effects and antifungal resistance, particularly when treatment is started before diagnosis is confirmed. They wanted to ensure that antifungal treatment would be stopped when investigations do not support a diagnosis of CAPA. However, the panel were aware that interpreting diagnostic test results and confirming a diagnosis of CAPA can be challenging. So, they recommended a multidisciplinary approach when deciding whether to stop treatment.

# 10. 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.

# 11. Palliative care

## 11.1 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.

## 11.2 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<br>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<br>The doses are based on the BNF and the Palliative care formulary |
|---|---|
| **Opioid** | 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<br>Midazolam 2.5 mg subcutaneously as required<br>(See the BNF for more details on dosages) |
| **Special considerations** | Consider concomitant use of an antiemetic and a regular stimulant laxative<br>Continue with non-pharmacological strategies for managing breathlessness when starting an opioid<br>Sedation and opioid use should not be withheld because of a fear of |

| Treatment | Dosage<br>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<br>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.

## 12. 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*

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*

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*

New

What risk factors in people who are critically ill and have, or have had, COVID-19 as part of their acute illness are associated with developing COVID-19-associated pulmonary aspergillosis (CAPA)?

*Suggested research details*

*Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness. Subgroups of particular interest include children and young people, and pregnant women.*

*Exposure: any*

*Outcomes:*

- *association of CAPA with individual factors (for example, age, sex, ethnicity, comorbidities, COVID-19 vaccination status,)*
- *association of CAPA with COVID-19 treatments (for example, respiratory support for COVID-19, high-dose corticosteroids, interleukin-6 inhibition)*
- *association of CAPA with length of stay in hospital*

New

What are the possible outcomes for people who are critically ill and have COVID-19-associated pulmonary aspergillosis (CAPA)?

*Suggested research details*

*Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and who have CAPA. Subgroups of particular interest: young people and children, pregnant women, ethnicity, immunosuppression and subgroups who have higher rates of COVID-19*

*Outcomes:*

- *presence of fungal serum biomarkers (for example galactomannan and beta-D-glucan)*
- *measures of inflammation (for example C-reactive protein)*
- *need for respiratory support (for example, invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO])*
- *hospitalisation metrics (for example, mortality, length of hospital stay, admission to and length of stay in intensive care)*
- *long-term morbidity outcomes, functional measures and patient outcomes*
- *results may be stratified (for example, disease severity, use of ECMO)*

New

In people with suspected COVID-19-associated pulmonary aspergillosis (CAPA), what are the most accurate tests for diagnosing the infection and when should they be done?

*Suggested research details*

*Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and suspected CAPA. Subgroups of particular interest include young people and children, and pregnant women.*

*Diagnostic tests:*

- *any methods used to diagnose pulmonary aspergillosis (for example, CT imaging, testing of bronchoalveolar lavage, non-bronchoscopic lavage, endotracheal aspirate, sputum samples, serum assays)*

*Reference standard:*

- *lung biopsy or postmortem diagnosis*

*Target condition:*

- *CAPA*

*Outcomes:*

- *sensitivity and specificity*
- *positive and negative likelihood ratios*

*Analysis:*

- *optimal time of diagnostic testing*

New

What are the views, preferences and experiences of people with COVID-19-associated pulmonary aspergillosis (CAPA), and their families or carers, on:

- available tests for diagnosing CAPA
- available treatments for CAPA?

*Suggested PIC (Population, Interest, Context)*

*P: people who have been diagnosed with and treated for CAPA, and their families or carers. Subgroups of particular interest include young people and children, and pregnant women.*

*I: tests for diagnosing CAPA and treatments for CAPA*

*C: people who have been diagnosed with, and had treatment for, CAPA in hospital*

New

What are the clinical and cost effectiveness, and the safety, of specific antifungal treatments for treating suspected or confirmed COVID-19-associated pulmonary aspergillosis (CAPA), and the optimal treatment duration? When should treatment be started, stopped or modified?

*Suggested PICO (Population, Intervention, Comparator, Outcome)*

*P: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness and have probable or diagnosed CAPA. Subgroups of particular interest: children and young people, pregnant women, ethnicity, immunosuppression, and subgroups who have higher rates of COVID-19.*

*I: voriconazole, isavuconazole, liposomal amphotericin B, posaconazole, echinocandins (for example, caspofungin, anidulafungin) and amphotericin B deoxycholate*

*C: Standard care (usually voriconazole)*

*O:*

- *all-cause mortality (at any time during treatment)*
- *number of people having 1 or more serious adverse events*
- *number of days without respiratory or organ support (organ support includes use of vasopressors and renal replacement therapy)*
- *length of stay in intensive care*
- *number of people having 1 or more adverse events*
- *treatment duration*
- *timing of starting treatment*
- *need for treatment modification*
- *length of hospital stays*
- *need for and duration of invasive mechanical ventilation*
- *need for switching, starting or restarting antifungal treatment*

# 13. Equality considerations

## 13.1 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.

## 13.2 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.

## 13.3 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.

## 14. 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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155. Neutralising antibodies for non-hospitalised adults, young people and children with COVID-19.

156. Neutralising antibodies for non-hospitalised adults, young people and children with COVID-19.

157. Neutralising antibodies for non-hospitalised adults, young people and children with COVID-19.

158. Neutralising antibodies for non-hospitalised adults, young people and children with COVID-19.

159. Neutralising antibodies for non-hospitalised adults, young people and children with COVID-19.