Australian guidelines for the clinical care of people with COVID-19
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Summary of recommendations

1 - Reading Guide
2 - Introduction
3 - Definition of disease severity

3.1 - Definition of disease severity for adults

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild illness</strong></td>
</tr>
<tr>
<td>Adults not presenting any clinical features suggestive of moderate or severe disease or a complicated course of illness.</td>
</tr>
<tr>
<td>Characteristics:</td>
</tr>
<tr>
<td>• no symptoms</td>
</tr>
<tr>
<td>• or mild upper respiratory tract symptoms</td>
</tr>
<tr>
<td>• or cough, new myalgia or asthenia without new shortness of breath or a reduction in oxygen saturation</td>
</tr>
<tr>
<td><strong>Moderate illness</strong></td>
</tr>
<tr>
<td>Stable adult patient presenting with respiratory and/or systemic symptoms or signs. Able to maintain oxygen saturation above 92% (or above 90% for patients with chronic lung disease) with up to 4 L/min oxygen via nasal prongs.</td>
</tr>
<tr>
<td>Characteristics:</td>
</tr>
<tr>
<td>• prostration, severe asthenia, fever &gt; 38°C or persistent cough</td>
</tr>
<tr>
<td>• clinical or radiological signs of lung involvement</td>
</tr>
<tr>
<td>• no clinical or laboratory indicators of clinical severity or respiratory impairment</td>
</tr>
<tr>
<td><strong>Severe illness</strong></td>
</tr>
<tr>
<td>Adult patients meeting any of the following criteria:</td>
</tr>
<tr>
<td>• respiratory rate ≥ 30 breaths/min</td>
</tr>
<tr>
<td>• oxygen saturation ≤ 92% at a rest state</td>
</tr>
<tr>
<td>• arterial partial pressure of oxygen (PaO2)/ inspired oxygen fraction (FiO2) ≤ 300</td>
</tr>
<tr>
<td><strong>Critical illness</strong></td>
</tr>
<tr>
<td>Adult patient meeting any of the following criteria:</td>
</tr>
<tr>
<td>Respiratory failure</td>
</tr>
<tr>
<td>• Occurrence of severe respiratory failure (PaO2/FiO2 &lt; 200), respiratory distress or acute respiratory distress syndrome (ARDS). This includes patients deteriorating despite advanced forms of respiratory support (NIV, HFNO) OR patients requiring mechanical ventilation.</td>
</tr>
<tr>
<td>OR other signs of significant deterioration</td>
</tr>
<tr>
<td>• hypotension or shock</td>
</tr>
<tr>
<td>• impairment of consciousness</td>
</tr>
<tr>
<td>• other organ failure</td>
</tr>
</tbody>
</table>
3.2 - Definition of disease severity for children and adolescents
These definitions apply to children under 16 years of age. Depending on the physical size and/or developmental status of the patient, either the paediatric or adult severity grading can be applied.

Cardiorespiratory and vital parameters must be considered within the normal age-appropriate ranges for neonates and children. If criteria fall across different severity classifications, use the more severe classification to manage illness.

<table>
<thead>
<tr>
<th></th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement$^\text{[1]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild illness</td>
<td>Normal or mildly reduced feeding</td>
<td>No or mild upper respiratory tract symptoms OR No or mild work of breathing</td>
<td>No supplemental oxygen required to maintain (\text{SpO}_2 &gt; 92%)</td>
</tr>
<tr>
<td>Moderate illness</td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids AND Normal conscious state</td>
<td>Moderate work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) but does not persistently breach Early Warning (e.g. MET) Criteria$^\text{[2]}$ OR Brief self-resolving apnoea (infants)</td>
<td>Requires low-flow oxygen (nasal prongs or mask) to maintain (\text{SpO}_2 &gt; 92%)</td>
</tr>
<tr>
<td>Severe illness</td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Drowsy / tired but easily rousable</td>
<td>Moderate-severe work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) with breaches of Early Warning / Medical Emergency Team criteria OR Apnoea needing support / stimulation (infants)</td>
<td>Requires high-flow oxygen at 2 L/kg/min$^\text{[3]}$ to maintain (\text{SpO}_2 &gt; 92%)</td>
</tr>
</tbody>
</table>
| Critical illness     | Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Altered conscious state / unconscious | Unable to maintain breathing or prevent apnoea without advanced modes of support OR Abnormal vital signs for age with persistent breaches of Early Warning (e.g. MET) Criteria OR Haemodynamically unstable without inotropic or vasopressor support OR Other organ failure | Requires advanced modes of support to maintain oxygenation

High-flow nasal oxygen at $> 2$ L/kg/min$^\text{[3]}$ OR Non-invasive ventilation OR Intubation and mechanical ventilation OR Extracorporeal membrane oxygenation (ECMO)
[1] Oxygen saturation target should be modified for patients with cyanotic heart disease.

[2] Temperature instability should be considered an abnormal vital sign in infants. Fever is common in children and does not contribute to determination of illness severity in isolation.

[3] Preterm infants and neonates < 4 kg may be managed on high-flow nasal cannula oxygen at 2-8 L/min irrespective of weight.

Note: co-morbidities (e.g. preterm infants, oncology, immunosuppressed, etc.) may increase the risk of more severe disease.

4 - Monitoring and markers of clinical deterioration

4.1 - Monitoring and markers of clinical deterioration

Consensus Recommendation

For people with COVID-19, monitor markers of clinical progression, such as rapidly progressive respiratory failure and sepsis, especially on days 5 to 10 after onset of symptoms.

5 - Disease-modifying treatments

5.1 - Dexamethasone

Weak Recommendation

Consider using dexamethasone 6 mg daily intravenous or oral for up to 10 days in adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

Interim awaiting complete reporting

The Taskforce is continually monitoring research on disease-modifying treatments. The recommendation will be revisited when more complete and detailed reporting of this comparison of the RECOVERY trial is made available [9]. As further evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).
5.2 - Baloxavir marboxil

**Strong Recommendation Against**

For people with COVID-19, only administer baloxavir marboxil in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

5.3 - Favipiravir

**Strong Recommendation Against**

For people with COVID-19, only administer favipiravir in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

5.4 - Lopinavir/ritonavir

**Strong Recommendation Against**

For people with COVID-19, only administer lopinavir/ritonavir in the context of randomised trials with appropriate ethical approval.

The Taskforce notes the release of the press statement from the chief investigators of the RECOVERY trial on 29 June that found no clinical benefit from using lopinavir-ritonavir in hospitalised patients with COVID-19. On 4 July WHO announced the lopinavir-ritonavir treatment arm of the Solidarity Trial had been discontinued with immediate effect. We await publication of the results of both trials.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).
5.5 - Remdesivir

5.5.1 - Remdesivir for adults

Weak Recommendation

Whenever possible remdesivir should be administered in the context of a randomised trial with appropriate ethical approval. Use of remdesivir for adults with moderate, severe or critical COVID-19 outside of a trial setting may be considered.

For information on dosages, length of treatment and characteristics of the patients in the trials used for this recommendation, see the Practical info tab below.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation.

5.5.2 - Remdesivir for pregnant patients

Weak Recommendation Against

Use of remdesivir for pregnant patients with COVID-19 outside of a trial setting should not be considered routinely.

As pregnant patients are often excluded from clinical trials, use of remdesivir in this population would be outside a clinical trial setting. Pregnant patients receiving remdesivir should nonetheless be enrolled in national COVID-19 registries. Currently, there is no direct evidence of the effects of remdesivir in pregnant and breastfeeding patients. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation.

5.5.3 - Remdesivir for children or adolescents

Weak Recommendation Against

Use of remdesivir for children or adolescents with COVID-19 outside of a trial setting should not be considered routinely.

If treatment is considered—in exceptional circumstances—it should be in consultation with a clinical reference group, such as the ANZPID COVID-19 Clinical Reference Group. Informed consent from parents/caregivers should also be obtained. Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation.
5.6 - Ruxolitinib

**Strong Recommendation Against**

For people with COVID-19, only administer ruxolitinib in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

5.7 - Chloroquine

**Strong Recommendation Against**

For people with COVID-19, only administer chloroquine in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

5.8 - Hydroxychloroquine

**Strong Recommendation Against**

For people with COVID-19, only administer hydroxychloroquine in the context of randomised trials with appropriate ethical approval.

The Taskforce notes the release of the press statement from the chief investigators of the RECOVERY trial on 5 June that found no clinical benefit from using hydroxychloroquine in hospitalised patients with COVID-19. On 4 July WHO announced the hydroxychloroquine treatment arm of the Solidarity Trial had been discontinued with immediate effect. We await publication of the results of both trials.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

5.9 - Convalescent plasma

**Strong Recommendation Against**

For people with COVID-19, only administer convalescent plasma in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).
5.10 - Interferon β-1a

**Strong Recommendation Against**

For people with COVID-19, only administer interferon β-1a in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

5.11 - Colchicine

**Strong Recommendation Against**

For adults with COVID-19, only administer colchicine in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

5.12 - Other disease-modifying treatments

**Consensus Recommendation**

For people with COVID-19, only administer disease-modifying treatments in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates regarding the use of these treatments, the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

6 - Chemoprophylaxis

6.1 - Hydroxychloroquine for post-exposure prophylaxis

**Strong Recommendation Against**

For people exposed to individuals with COVID-19, only administer hydroxychloroquine for post-exposure prophylaxis in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on chemoprophylaxis. As evidence accumulates the Taskforce will continue to review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).
7 - Respiratory support

**Guiding principles of care**

For patients with COVID-19 for whom respiratory support (HFNO/NIV) is being considered, decisions should balance likelihood of patient benefit against the risk of infection for healthcare workers. For patients with COVID-19 receiving respiratory support (HFNO/NIV) or requiring intubation, use single rooms or negative pressure rooms wherever possible and ensure contact, droplet and airborne precautions are in place.

The relative risk of infection to healthcare workers associated with specific oxygen therapies remains uncertain and may vary from site to site.

7.1 - High-flow nasal oxygen therapy

**Recommendation Strength Not Set**

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where oxygen is delivered, often in conjunction with compressed air and humidification. It delivers high flow oxygen via large diameter nasal cannula that is humidified and heated. Flow rates can be given up to 60 L/min in adults and 25 L/min in children with an oxygen/air blender supplying oxygen at 21-100%.

High-flow humidified oxygen should be considered when unable to maintain SaO2 ≥ 92% despite conventional oxygen delivery at > 6 L/min or an FiO2 0.4.

**Strong Recommendation**

In [negative pressure rooms](#), use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.

**Weak Recommendation**

In [single rooms](#) or [shared ward spaces with cohorting of confirmed COVID-19 patients only](#), consider using high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.

**Strong Recommendation Against**

In [shared wards](#) or [emergency department cubicles](#) do not use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19.
Strong Recommendation Against

During **inter-hospital patient transfer/retrieval** do not use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19.

### 7.2 - Non-invasive ventilation

**Recommendation Strength Not Set**

Non-invasive ventilation (NIV), also known as non-invasive positive pressure ventilation (NIPPV) or bilevel positive pressure support (BiPAP), is a form of respiratory support. Bilevel positive pressure is delivered throughout the respiratory cycle by a firm-fitting nasal-face mask. The patient breathes spontaneously and triggers the device to cycle.

A higher level of pressure is provided during the inspiratory phase to enhance ventilation, while a lower level of continuous positive pressure is delivered during the expiratory phase (also known as positive end-expiratory pressure or PEEP). Supplemental oxygen can also be delivered through the device.

**Consensus Recommendation**

In **negative pressure rooms**, consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

**Consensus Recommendation**

In **single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only**, consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

**Consensus Recommendation**

In **shared wards or emergency department cubicles**, do not use NIV therapy for patients with hypoxaemia associated with COVID-19.

**Consensus Recommendation**


**Consensus Recommendation**

In patients with COVID-19 for whom NIV is appropriate for an alternate clinical presentation (e.g. concomitant COPD with type 2 respiratory failure and hypercapnoea, APO), ensure airborne and other infection control precautions are optimised.
7.3 - Respiratory management of the deteriorating patient

Consensus Recommendation

In patients with COVID-19 who are deteriorating, consider early endotracheal intubation and invasive mechanical ventilation.

Patients can deteriorate rapidly 5 to 10 days after onset of symptoms.

7.4 - Videolaryngoscopy

Weak Recommendation

In adults with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy if available and the operator is trained in its use.

7.5 - Neuromuscular blockers

Recommendation Strength Not Set

Neuromuscular blocking agents (NMBAs) are a pharmaceutical intervention that may facilitate protective lung ventilation in patients who are mechanically ventilated with moderate to severe acute respiratory distress syndrome (ARDS). NMBAs may reduce patient-ventilator dyssynchrony and facilitate improved oxygenation by various mechanisms, including reducing the inspiratory muscle effort and the work of breathing, and reducing ventilator-induced lung injury.

Weak Recommendation Against

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs).

However, if protective lung ventilation cannot be achieved, consider using NMBAs for up to 48 hours. If indicated, consider cisatracurium as first-line agent, if cisatracurium is not available alternatives include atracurium or vecuronium by infusion.

7.6 - Positive end-expiratory pressure

Consensus Recommendation

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, consider using a higher PEEP strategy (PEEP > 10 cm H2O) over a lower PEEP strategy.
### 7.7 - Prone positioning

<table>
<thead>
<tr>
<th>Recommendation</th>
<th><strong>Strength Not Set</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positioning the patient in a face-down (prone) position may help to open up (recruit) collapsed alveoli and improve oxygen levels in the blood.</td>
<td></td>
</tr>
</tbody>
</table>

**Consensus Recommendation**

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning.

*Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff, and that minimises the risk of adverse events, e.g. accidental extubation.*

**Consensus Recommendation**

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning. When positioning a patient in prone, ensure it is used with caution and close monitoring of the patient. Patients who are deteriorating should be considered for early endotracheal intubation and invasive mechanical ventilation.

### 7.8 - Recruitment manoeuvres

<table>
<thead>
<tr>
<th>Recommendation</th>
<th><strong>Strength Not Set</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving respiratory support are at an increased risk of lung injury. Recruitment manoeuvres are used to open up ('recruit') collapsed alveoli and are a common element of an ‘open lung approach’ to protect the lungs during mechanical ventilation. The manoeuvres use a sustained increase in airway pressure to re-open collapsed alveoli.</td>
<td></td>
</tr>
</tbody>
</table>

Types of manoeuvres include: prolonged high continuous positive airway pressure; progressive incremental increases in positive end-expiratory pressure at a constant driving pressure (incremental PEEP, stepwise or staircase); and high driving pressures.

**Consensus Recommendation**

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider using recruitment manoeuvres.

*If recruitment manoeuvres are used, do not use staircase or stepwise (incremental PEEP) recruitment manoeuvres.*
7.9 - Extracorporeal membrane oxygenation

**Recommendation Strength Not Set**

Extracorporeal membrane oxygenation (ECMO) is a form of life support that removes blood from the body via large cannulae, oxygenates and removes carbon dioxide from the blood external to the patient, and then returns the blood to the body. Venovenous (VV) ECMO provides oxygenation support for the lungs only, while venoarterial (VA) ECMO supports the heart and lungs.

**Consensus Recommendation**

In mechanically ventilated adults with COVID-19 and refractory hypoxaemia (despite optimising ventilation, use of rescue therapies and proning), consider using venovenous extracorporeal membrane oxygenation (VV ECMO) if available, or referring the patient to an ECMO centre.

Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in carefully selected patients with COVID-19 and severe ARDS.

8 - Steroids for people with asthma or COPD and COVID-19

8.1 - Steroids for people with asthma or COPD and COVID-19

**Consensus Recommendation**

Use inhaled or oral steroids for the management of people with co-existing asthma or COPD and COVID-19 as you would normally for viral exacerbation of asthma or COPD. Do not use a nebuliser.

9 - Anticoagulants

9.1 - Venous thromboembolism (VTE) prophylaxis

**Consensus Recommendation**

Use prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) in adults with moderate COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding. Where severe acute kidney disease is present, unfractionated heparin or renally adjusted doses of LMWH may be used (e.g. enoxaparin 20 mg once daily or dalteparin 2500 IU once daily).
9.2 - Increased-dose venous thromboembolism (VTE) prophylaxis

**Consensus Recommendation**

Consider using increased prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily) in adults with severe or critical COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding or platelet count < 30 x 10^9/L. Where severe acute kidney disease is present (creatinine clearance < 30 mL/min), unfractionated heparin or renal adjusted doses of LMWH may be used (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily).

10 - ACEIs/ARBs in patients with COVID-19

10.1 - ACEIs/ARBs in patients with COVID-19

**Consensus Recommendation**

In patients with COVID-19 who are receiving ACEIs/ARBs, these medications should be continued unless contraindicated (e.g. hypotension).

11 - Pregnancy and perinatal care

11.1 - Mode of birth

**Weak Recommendation**

For pregnant women with COVID-19, mode of birth should remain as per usual care.

There is currently no evidence to indicate that caesarean section for women with COVID-19 reduces the risk of vertical transmission to the newborn. Mode of birth should continue as per usual care. Respiratory deterioration due to COVID-19 may prompt urgent delivery on an individual basis.

11.2 - Breastfeeding

**Weak Recommendation**

Breastfeeding is supported irrespective of the presence of COVID-19. However, women with COVID-19 who are breastfeeding should use infection control and prevention measures (mask and hand hygiene) while infectious.

There is currently no evidence to indicate that breastfeeding increases the risk of vertical transmission to the newborn. There are substantial known benefits for breastfeeding and therefore women should be supported to initiate or continue breastfeeding.

12 - Methods and Processes
13 - Conflicts of Interest
14 - Abbreviations and Acronyms
1 - Reading Guide

The treatment of novel coronavirus disease 2019 (COVID-19) is a rapidly expanding area of research, with an unprecedented global effort underway to combat this disease. As a result, recommendations based on current evidence are likely to become outdated quickly as new primary studies are published. The living evidence approach facilitates rapid updating of recommendations. By frequently incorporating the most up-to-date evidence, these methods ensure that the currency of each recommendation remains high.

It is anticipated that these living recommendations will be updated weekly as and when new evidence is available. This will be reflected in the publication of a new version in which changes made to a specific recommendation or supporting information are highlighted to emphasise the update.

The guideline consists of two layers:

1. The Recommendation

   Recommendation for (Green)
   A strong recommendation is given when there is high-certainty evidence 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 showing that the overall disadvantages of the intervention are clearly greater than the benefits. 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 disadvantages of the intervention are greater than the benefits, but where this is not substantiated by strong evidence. This recommendation is also used where there is strong evidence of both beneficial and harmful effects, but where the balance between them is difficult to determine. Likewise, it is also used when patient preferences vary.

   Consensus Recommendation (Bluish-Purple)
   A consensus recommendation can be given for or against the intervention. 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. Note that early recommendations are primarily adapted from other guidelines and/or based on the consensus of the guideline panel, and supporting information will be limited. Additional information will be added as recommendations are updated in light of new evidence.

Evidence profile: The overall effect estimates and references to the studies.
Summary: Overview and brief review of the underlying evidence.
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 significantly different.
- Low: We have limited confidence in the estimated effect. The true effect may be significantly different from the estimated effect.
- Very low: We have very little confidence in the estimated effect. The true effect is likely to be significantly different from that estimated effect.

Key information: Brief description of beneficial and harmful effects, certainty of evidence and considerations of patient preferences.
Rationale: Description of how the above elements were weighted in relation to each other and resulted in the current recommendation direction and strength.
Practical information: Practical information regarding the treatment and information on any special patient considerations.
Adaption: If the recommendation is adapted from another guideline you can find more information here.
Feedback: If you are logged in as a user, you can comment here on specific recommendations. See here for guidance on how to log in.
References: Reference list for the recommendation.

The gradation of evidence quality and recommendation strength used is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE). For a quick and informative introduction to GRADE, the article Understanding GRADE: an introduction by Goldet & Howick is recommended (J Evid Based Med 2013;6(1):50-4). See also http://www.gradeworkinggroup.org.
2 - Introduction

Introduction

Novel coronavirus disease 2019 (COVID-19) is an infectious disease caused by the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since its identification in December 2019, COVID-19 has spread around the world and was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on 30 January 2020 [1]. People infected with the COVID-19 virus are most likely to only experience mild symptoms and recover without requiring special treatment. However, some people will experience moderate or severe disease. Older people and those with underlying diseases or medical conditions (such as cardiovascular disease, diabetes, chronic respiratory disease and cancer) are more likely to develop serious illness that require special care and treatment [58].

Clinical guidelines are integral to ensuring that healthcare decisions are based on the best available evidence. Since the emergence of the COVID-19 pandemic, many national and international organisations have released guidelines related to different aspects of the management of people with COVID-19. With the support of the National Health and Medical Research Council (NHMRC), the National COVID-19 Clinical Evidence Taskforce was established to develop (in partnership with a range of national professional societies and organisations) living guidelines for clinical management and care of people with suspected or confirmed COVID-19.

The recommendations within this guideline were developed in collaboration with:
- Australian Living Evidence Consortium (Coordinating Lead)
- Cochrane Australia (Secretariat)
- Australasian Association of Academic Primary Care
- Australasian College for Emergency Medicine
- Australasian College for Infection Prevention and Control
- Australasian Sleep Association
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
- Australasian Society for Infectious Diseases
- Australian Association of Gerontology
- Australian College of Critical Care Nurses
- Australian College of Midwives
- Australian College of Nursing
- Australian College of Rural and Remote Medicine
- Australian COVID-19 Palliative Care Working Group
- Australian and New Zealand College of Anaesthetists
- Australian and New Zealand Intensive Care Society
- Australian and New Zealand Society for Geriatric Medicine
- Australian Primary Health Care Nurses Association
- Australian Resuscitation Council
- Australian Society of Anaesthetists
- College of Emergency Nursing Australasia
- CRANAPlus
- National Aboriginal Community Controlled Health Organisation
- Royal Australasian College of Physicians
- Royal Australian College of General Practitioners
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists
- Society of Hospital Pharmacists of Australia
- Thoracic Society of Australia and New Zealand
- Thrombosis and Haemostasis Society of Australia and New Zealand

Updating and public consultation

A considerable volume of research related to the care of people with COVID-19 is ongoing and will potentially impact clinical recommendations. To ensure these guidelines are updated rapidly in response to new and important evidence, the underpinning knowledge syntheses and recommendations will be reviewed and updated on an ongoing basis. It is anticipated that these living recommendations will be updated weekly as and when new evidence is available. This will be reflected in the publication of a new version in which changes made to a specific recommendation or supporting information are highlighted in order to emphasise the update.

The consortium is seeking NHMRC approval of the guideline under section 14A of the National Health and Medical Research Council Act 1992. As part of the approval process (and for the lifetime of the guidelines), public consultation is required. We welcome your feedback and suggestions. Comments can be submitted via the feedback function under each recommendation in MAGIC, see the reading guide in the above section for guidance, or by emailing guidelines@covid19evidence.net.au.

Purpose

The purpose of this guideline is to provide health professionals and patients with up-to-date, evidence-based recommendations to guide shared decision-making in the treatment of COVID-19. The guideline contains specific and actionable recommendations for selected, well-defined clinical problems (i.e. what needs to be done and who it is relevant to). It does not define the individuals responsible for providing care, nor does it consider the social or economic implications of guideline adherence.

Scope

This guideline aims to provide specific, patient-focused recommendations on management and care of people with suspected or confirmed COVID-19. With the exception of chemoprophylaxis for the prevention of infection in people exposed to COVID-19, the guideline does not include other interventions used in the prevention of COVID-19 infection or transmission. Within each recommendation, the patient population of interest is specified.

Target audience

These recommendations are applicable to individuals responsible for the care of people with COVID-19. These include health professionals, individuals providing support and education to people with COVID-19, and people with diagnosed or suspected COVID-19 themselves.

Individuals such as policy makers, practice managers, researchers and students may elect to use or adopt these recommendations for purposes other than the treatment of COVID-19; however these individuals do not represent the target audience. Additional considerations not addressed within this guideline are required when using these recommendations for any purpose other than for the treatment or support of individuals with COVID-19.

How to cite this guideline
3 - Definition of disease severity

3.1 - Definition of disease severity for adults

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild illness</strong></td>
</tr>
</tbody>
</table>
| Adults not presenting any clinical features suggestive of moderate or severe disease or a complicated course of illness.  
Characteristics:  
• no symptoms  
• or mild upper respiratory tract symptoms  
• or cough, new myalgia or asthenia without new shortness of breath or a reduction in oxygen saturation |
| **Moderate illness**     |
| Stable adult patient presenting with respiratory and/or systemic symptoms or signs. Able to maintain oxygen saturation above 92% (or above 90% for patients with chronic lung disease) with up to 4 L/min oxygen via nasal prongs.  
Characteristics:  
• prostration, severe asthenia, fever > 38°C or persistent cough  
• clinical or radiological signs of lung involvement  
• no clinical or laboratory indicators of clinical severity or respiratory impairment |
| **Severe illness**       |
| Adult patients meeting any of the following criteria:  
• respiratory rate ≥ 30 breaths/min  
• oxygen saturation ≤ 92% at a rest state  
• arterial partial pressure of oxygen (PaO2)/ inspired oxygen fraction (FiO2) ≤ 300 |
| **Critical illness**     |
| Adult patient meeting any of the following criteria:  
Respiratory failure  
• Occurrence of severe respiratory failure (PaO2/FiO2 < 200), respiratory distress or acute respiratory distress syndrome (ARDS). This includes patients deteriorating despite advanced forms of respiratory support (NIV, HFNO) OR patients requiring mechanical ventilation.  
OR other signs of significant deterioration  
• hypotension or shock  
• impairment of consciousness  
• other organ failure |

Adaptation

The definitions of disease severity are adapted from published definitions from China [2], Italy [3] and Alfred Health (Melbourne) [4].
3.2 - Definition of disease severity for children and adolescents
These definitions apply to children under 16 years of age. Depending on the physical size and/or developmental status of the patient, either the paediatric or adult severity grading can be applied.

Cardiorespiratory and vital parameters must be considered within the normal age-appropriate ranges for neonates and children. If criteria fall across different severity classifications, use the more severe classification to manage illness.

<table>
<thead>
<tr>
<th>Mild illness</th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal or mildly reduced feeding</td>
<td>No or mild upper respiratory tract symptoms OR No or mild work of breathing</td>
<td>No supplemental oxygen required to maintain SpO$_2$ &gt; 92%</td>
</tr>
<tr>
<td>Moderate illness</td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids AND Normal conscious state</td>
<td>Moderate work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) but does not persistently breach Early Warning (e.g. MET) Criteria[2] OR Brief self-resolving apnoea (infants)</td>
<td>Requires low-flow oxygen (nasal prongs or mask) to maintain SpO$_2$ &gt; 92%</td>
</tr>
<tr>
<td>Severe illness</td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Drowsy / tired but easily rousable</td>
<td>Moderate-severe work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) with breaches of Early Warning / Medical Emergency Team criteria OR Apnoea needing support / stimulation (infants)</td>
<td>Requires high-flow oxygen at 2 L/kg/min[3] to maintain SpO$_2$ &gt; 92%</td>
</tr>
<tr>
<td>Critical illness</td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Altered conscious state / unconscious</td>
<td>Unable to maintain breathing or prevent apnoea without advanced modes of support OR Abnormal vital signs for age with persistent breaches of Early Warning (e.g. MET) Criteria OR Haemodynamically unstable without inotropic or vasopressor support OR Other organ failure</td>
<td>Requires advanced modes of support to maintain oxygenation High-flow nasal oxygen at &gt; 2 L/kg/min[3] OR Non-invasive ventilation OR Intubation and mechanical ventilation OR Extracorporeal membrane</td>
</tr>
</tbody>
</table>

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[1] Early Warning Criteria (MET) criteria
[2] Moderate work of breathing includes shortness of breath, increased respiratory rate, or need for supplemental oxygen.
[3] High-flow nasal oxygen is defined as > 2 L/kg/min.
[1] Oxygen saturation target should be modified for patients with cyanotic heart disease.
[2] Temperature instability should be considered an abnormal vital sign in infants. Fever is common in children and does not contribute to determination of illness severity in isolation.
[3] Preterm infants and neonates < 4 kg may be managed on high-flow nasal cannula oxygen at 2-8 L/min irrespective of weight.

Note: co-morbidities (e.g. preterm infants, oncology, immunosuppressed, etc.) may increase the risk of more severe disease.
4 - Monitoring and markers of clinical deterioration

4.1 - Monitoring and markers of clinical deterioration

Consensus Recommendation

For people with COVID-19, monitor markers of clinical progression, such as rapidly progressive respiratory failure and sepsis, especially on days 5 to 10 after onset of symptoms.

Adaptation

The recommendation for monitoring and markers of clinical deterioration is adapted from published recommendations by the World Health Organization [58], National Institute for the Infectious Diseases (Italy) [3] and Surviving Sepsis Campaign [56]. Wording has been adapted for clarity and applicability to the Australian context.
5 - Disease-modifying treatments

Several classes of therapies are currently under investigation to determine their effectiveness in treating COVID-19. These include, but are not limited to, antivirals (remdesivir, lopinavir and ritonavir), antimalarials (hydroxychloroquine and chloroquine), interleukin receptor agonists (tocilizumab and anakinra), corticosteroids and convalescent plasma. The categories of disease-modifying treatments being considered can be seen in the table below. We are continually monitoring new research for randomised trials that evaluate any disease-modifying treatments for COVID-19.

While national and international guidelines published early in the pandemic did not support the use of disease-modifying therapies in treating people with COVID-19 (except in the context of clinical trials), this is now changing as evidence for certain treatments emerges.

<table>
<thead>
<tr>
<th>Category</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents that may have activity against SARS-CoV-2</td>
<td>Antimalarials, Antivirals, Convalescent plasma</td>
</tr>
<tr>
<td>Agents that may have activity against the associated cytokine-release syndrome</td>
<td>Tocilizumab, Anakinra (IL1RA), Corticosteroids</td>
</tr>
<tr>
<td>Other and ancillary agents</td>
<td>ACE inhibitors, NSAIDs</td>
</tr>
<tr>
<td>Blood purification systems for reducing cytokines in ICU</td>
<td>Cytokine removal</td>
</tr>
</tbody>
</table>

5.1 - Dexamethasone

Consider using dexamethasone 6 mg daily intravenous or oral for up to 10 days in adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

Interim awaiting complete reporting

The Taskforce is continually monitoring research on disease-modifying treatments. The recommendation will be revisited when more complete and detailed reporting of this comparison of the RECOVERY trial is made available [9]. As further evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms

In patients receiving oxygen or invasive mechanical ventilation, all-cause mortality is reduced with dexamethasone. The trial on which this recommendation is based has not yet reported on adverse events or serious adverse events. However, the panel believes that the mortality benefit outweighs potential harms associated with adverse events.

Certainty of the Evidence

Certainty of the evidence for mortality in patients receiving oxygen or invasive mechanical ventilation is moderate based on the reliance on a single study that is yet to be peer reviewed. Patients and personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect reported outcomes.
Preference and values
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there are mortality benefits most patients would opt for dexamethasone.

Resources and other considerations
Dexamethasone is widely available and affordable. Use of dexamethasone in patients with COVID-19 who are receiving supplementary oxygen or invasive ventilation is unlikely to have an impact on availability of this drug for other indications.

Equity
We have no systematically collected direct evidence regarding impact on equity. Since dexamethasone is widely available and affordable, no negative impact is expected.

Acceptability
Dexamethasone is likely to be acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.

Feasibility
Dexamethasone is likely to be feasible because it is already widely used for other indications. There are no known issues with availability of this drug.

Rationale
Due to a reduction in all-cause mortality, along with no important resource implications and the likely acceptability of the drug, we recommend that use of dexamethasone be considered for adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

The conditional recommendation reflects that complete reporting of the results of the RECOVERY Trial are not yet available [9].

Clinical Question/ PICO
- **Population:** Patients with COVID-19
- **Intervention:** Dexamethasone
- **Comparator:** Standard care

Summary
Preliminary evidence indicates that dexamethasone probably decreases all-cause mortality in COVID-19 patients who require oxygen or invasive mechanical ventilation. In contrast, dexamethasone in patients who do not require oxygen may lead to increased mortality.

Evidence informing this recommendation comes from a single, open-label randomised trial currently only available as a preprint [9] that compared dexamethasone plus usual care to usual care alone in 6,425 hospitalised patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Patients were originally restricted to adults 18 years of age or older, however this restriction was removed during recruitment. Six pregnant or breastfeeding women were included in the analyses, however it is unclear to which treatment arm they were assigned. Complete reporting of this trial is not yet available.
Outcomes reported include 28-day mortality, duration of hospital stay, number of patients discharged from hospital after 28 days, and the number of patients requiring mechanical ventilation. For mortality, subgroup analyses were conducted based on whether patients did not require oxygen, required oxygen, or required mechanical ventilation. The study has not yet reported on adverse events, serious adverse events or discontinuation of treatment due to adverse events.

Certainty of the evidence for all-cause mortality for patients not receiving oxygen is low. This judgement is based on serious imprecision due to the reliance on a single study and non-significant findings when the data were adjusted for age. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect this outcome.

Certainty of the evidence for all-cause mortality for patients receiving oxygen or receiving invasive mechanical ventilation is moderate. This judgement is based on reliance on a single study. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect this outcome.

Overall certainty of the evidence for other outcomes (mechanical ventilation requirement; discharge from hospital; duration of hospital stay) is moderate.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality (patients who received no oxygen)</strong> Within 28 days after commencing treatment</td>
<td>Relative risk 1.28 (CI 95% 1 - 1.64) Based on data from 1,535 patients in 1 studies.</td>
<td>132 per 1000</td>
<td>Low Due to very serious imprecision</td>
<td>Dexamethasone may increase all-cause mortality in patients who receive no oxygen (total no of events = 222)</td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td>169 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: 37 more per 1000 ( CI 95% 0 fewer - 84 more )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality (patients who received oxygen only)</strong> Within 28 days after commencing treatment</td>
<td>Relative risk 0.86 (CI 95% 0.76 - 0.98) Based on data from 3,883 patients in 1 studies.</td>
<td>250 per 1000</td>
<td>Moderate Due to only one study</td>
<td>Dexamethasone probably decreases all-cause mortality in patients who receive oxygen only (total no of events = 925)</td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td>215 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: 35 fewer per 1000 ( CI 95% 60 fewer - 5 fewer )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality (patients who received invasive mechanical ventilation)</strong> Within 28 days</td>
<td>Relative risk 0.71 (CI 95% 0.59 - 0.86) Based on data from 1,007 patients in 1 studies.</td>
<td>407 per 1000</td>
<td>Moderate Due to only one study</td>
<td>Dexamethasone probably decreases all-cause mortality in patients who receive invasive mechanical ventilation (total no of events = 372)</td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td>289 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: 118 fewer per 1000 ( CI 95% 167 fewer - 57 fewer )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of bias:** No 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. **Imprecision:** Very Serious. Only data from one study, wide confidence intervals.


4. **Risk of bias:** No 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. **Imprecision:** Serious. Only data from one study.


6. **Risk of bias:** No 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. **Imprecision:** Serious. Only data from one study.


8. **Risk of bias:** No 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. **Imprecision:** Serious. Only data from one study.

9. **Mechanical ventilation requirement** Within 28 days after commencing treatment.

   - **Baseline/comparator:** Control arm of reference used for intervention.
   - **Risk of bias:** No 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. **Imprecision:** Serious. Only data from one study.
   - Relative risk 0.93 (CI 95% 0.84 - 1.02) Based on data from 5,418 patients in 1 studies. (Randomized controlled)
   - **Relative risk:** 0.93
   - **CI 95%:** 0.84 - 1.02
   - **Difference:** 18 fewer per 1000
   - **CI 95%:** 41 fewer - 5 more
   - **Type:** (Randomized controlled)
   - **Moderate** Due to only one study
   - **Dexamethasone probably decreases need for mechanical ventilation requirement slightly**

10. **Discharge from hospital** Within 28 days after commencing treatment.

    - **Baseline/comparator:** Control arm of reference used for intervention.
    - **Risk of bias:** No 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. **Imprecision:** Serious. Only data from one study.
    - Relative risk 1.06 (CI 95% 1.02 - 1.1) Based on data from 6,425 patients in 1 studies. (Randomized controlled)
    - **Relative risk:** 1.06
    - **CI 95%:** 1.02 - 1.1
    - **Difference:** 37 more per 1000
    - **CI 95%:** 12 more - 61 more
    - **Type:** (Randomized controlled)
    - **Moderate** Due to only one study
    - **Dexamethasone probably increases number of patients discharged from hospital within the first 28 days**

11. **Duration of hospital stay** Time to discharge after commencing treatment (Days) (Randomized controlled)

    - **Baseline/comparator:** Control arm of reference used for intervention.
    - **Risk of bias:** No 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. **Imprecision:** Moderate. Only data from one study.
    - **Relative risk:** 1.06
    - **CI 95%:** 1.02 - 1.1
    - **Difference:** 37 more per 1000
    - **CI 95%:** 12 more - 61 more
    - **Type:** (Randomized controlled)
    - **Moderate** Due to only one study
    - **Dexamethasone probably makes no difference to duration of hospital stay**
Weak Recommendation Against
Do not routinely use dexamethasone to treat COVID-19 in adults who do not require oxygen.

Interim awaiting complete reporting
Dexamethasone may still be considered for other evidence-based indications in people who have COVID-19.

The Taskforce is continually monitoring research on disease-modifying treatments. The recommendation will be revisited when more complete and detailed reporting of this comparison of the RECOVERY trial is made available (9). As further evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms
In patients who do not require oxygen, all-cause mortality may be higher with dexamethasone. The trial on which this recommendation is based has not yet reported on adverse events or serious adverse events.

Certainty of the Evidence
Certainty of the evidence for mortality in patients who do not require oxygen is low based on very serious imprecision due to the reliance on a single study and the difference in the relative risk when using adjusted versus non-adjusted analysis. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect reported outcomes.

Preference and values
We have no systematically collected information regarding patients’ preferences and values.

Resources and other considerations
There are no identified resource issues as the recommendation reflects usual care.

Equity
No important issues with the recommended alternative.


In patients who do not require oxygen, all-cause mortality may be higher with dexamethasone. The trial on which this recommendation is based has not yet reported on adverse events or serious adverse events.

Important harms

Certainty of the evidence for mortality in patients who do not require oxygen is low based on very serious imprecision due to the reliance on a single study and the difference in the relative risk when using adjusted versus non-adjusted analysis. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect reported outcomes.

Substantial variability is expected or uncertain

No important issues with the recommended alternative

No important issues with the recommended alternative
Rationale
Evidence suggests that the use of dexamethasone in patients with COVID-19 who do not require oxygen may increase the risk of all-cause mortality. We therefore recommend against the use of dexamethasone in this population, unless there is an alternative evidence-based indication for its use.

The conditional recommendation reflects that complete reporting of the results of the RECOVERY Trial are not yet available [9].

Acceptability
We have no systematically collected evidence regarding acceptability.

Feasibility
There are no identified feasibility issues as the recommendation reflects usual care.

Clinical Question/ PICO
Population: Patients with COVID-19 who do not require oxygen
Intervention: Dexamethasone
Comparator: Standard Care

Summary
See summary for 'Patients with COVID-19 - Dexamethasone vs Standard care'

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timeframe</td>
<td></td>
<td>Standard care</td>
<td>Dexamethasone</td>
<td></td>
</tr>
<tr>
<td>See evidence profile for 'Patients with COVID-19 - Dexamethasone vs Standard care'</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.2 - Baloxavir marboxil

**Strong Recommendation Against**

For people with COVID-19, only administer baloxavir marboxil in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

**Key Info**

**Benefits and harms**

In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms associated with the use of baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache.

**Certainty of the Evidence**

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Because the benefit to harm ratio is uncertain, it is worth noting that this recommendation will protect more vulnerable populations, such as children.

**Acceptability**

Treatment is probably acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.

**Feasibility**

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Rationale**

There is currently limited evidence about the impact of baloxavir marboxil on patient-relevant outcomes in COVID-19.
The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that this treatment should only be administered in the context of randomised trials with appropriate ethical approval.

**Clinical Question/ PICO**

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Baloxavir marboxil</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

**Summary**

Evidence informing this recommendation comes from a single randomised trial that compared baloxavir marboxil to standard care in patients with COVID-19 [43]. The study included 20 hospitalised adults concomitantly using lopinavir/ritonavir, darunavir/cobicistat and/or arbidol.

The study results are only available as a preprint paper (posted to medRxiv on 5 May 2020) and have therefore not been peer-reviewed. We follow up with the corresponding author every two months to request an update on the study's publication status.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

The Therapeutic Goods Administration highlights several mild side effects associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache. In addition, post-marketing surveillance has identified cases of anaphylactic reactions, angioedema, vomiting and other gastrointestinal and skin/subcutaneous tissue disorders [44].

Based on the available evidence, there remains significant uncertainty whether baloxavir marboxil is more effective and safer than standard care in treating patients with COVID-19.

### Table: Comparative Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During treatment (14 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Based on data from 20 patients in 1 studies.</td>
<td></td>
<td></td>
<td>There were no deaths in the study</td>
</tr>
<tr>
<td><strong>Respiratory support and ARDS</strong></td>
<td>Odds Ratio 2.25 (CI 95% 0.38 - 13.47)</td>
<td>400 per 1000</td>
<td>Very Low (Quality of evidence)</td>
<td>We are uncertain whether baloxavir marboxil increases or decreases respiratory support and ARDS (total no of events = 10)</td>
</tr>
<tr>
<td>During treatment (14 days)</td>
<td>Based on data from 20 patients in 1 studies.</td>
<td>600 per 1000</td>
<td>Due to serious risk of bias and very serious imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td>Difference: 200 more per 1000 ( CI 95% 198 fewer - 500 more )</td>
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</tr>
</tbody>
</table>
| **Mechanical ventilation or ECMO**  
During treatment (14 days) | Odds Ratio 3.32  
(CI 95% 0.12 - 91.6)  
Based on data from 20 patients in 1 studies.  
(Randomized controlled) | *0 fewer* per 1000  
(Difference: 0 fewer per 1000  
(CI 95% 0 fewer - 0 fewer)) |
|   |   | Very Low  
Due to serious risk of bias and very serious imprecision |
| There were too few who required mechanical ventilation or ECMO to determine whether baloxavir marboxil makes a difference (total no of events = 1) |   |   |
|   |   |   |
| **Serious adverse events**  
During treatment (14 days) |   |   |
| 9 Critical |   |   |
|   |   |   |
| **Adverse events**  
During treatment (14 days) |   |   |
| 6 Important |   |   |
|   |   |   |
| **Clinical improvement**  
End of treatment (14 days) | Odds Ratio 1.5  
(CI 95% 0.26 - 8.82)  
Based on data from 20 patients in 1 studies.  
(Randomized controlled) | **500** per 1000  
(Difference: 100 more per 1000  
(CI 95% 294 fewer - 398 more)) |
|   |   | Very Low  
Due to serious risk of bias and very serious imprecision |
| We are uncertain whether baloxavir marboxil increases or decreases clinical improvement (total no of events = 11) |   |   |
|   |   |   |

3. **Risk of bias**: Serious. **Imprecision**: Very Serious. Low number of patients. Only data from one study.
5. **Risk of bias**: Serious. **Imprecision**: Very Serious. Low number of patients. Only data from one study.
7. Systematic review [42] with included studies: [43]. **Baseline/comparator**: Control arm of reference used for intervention.
5.3 - Favipiravir

Strong Recommendation Against

For people with COVID-19, only administer favipiravir in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms

The safety profile for favipiravir is incompletely characterised in humans. As a result, there is uncertainty around the benefits and harms for patients with COVID-19.

Certainty of the Evidence

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

Preference and values

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Because the benefit to harm ratio is uncertain, it is worth noting that this recommendation will protect more vulnerable populations, such as children.

Acceptability

Treatment is probably acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

There is currently limited evidence about the impact of favipiravir on patient-relevant outcomes in COVID-19.
The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that this treatment should only be administered in the context of randomised trials with appropriate ethical approval.

### Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with COVID-19</td>
<td>Favipiravir</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

### Summary

Evidence informing this recommendation comes from a single randomised trial that compared favipiravir to standard care in patients with COVID-19 [43]. The study included 19 hospitalised adults concomitantly using lopinavir/ritonavir, darunavir/ cobicistat and/or arbidol.

The study results are only available as a preprint paper (posted to medRxiv on 5 May 2020) and have therefore not been peer-reviewed. We follow up with the corresponding author every two months to request an update on the study's publication status.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

As of 6 May 2020, favipiravir (Avigan) is not approved for use in Australia. The safety profile for favipiravir is incompletely characterised in humans.

Based on the available evidence, there remains significant uncertainty whether favipiravir is more effective and safer than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>During treatment (14 days)</td>
<td>Based on data from 19 patients in 1 studies. ¹ (Randomized controlled)</td>
<td>⁴</td>
<td>²</td>
<td>There were no deaths in the study</td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>During treatment (14 days)</td>
<td>Odds Ratio 1.2 (CI 95% 0.19 - 7.44) Based on data from 19 patients in 1 studies. ³ (Randomized controlled)</td>
<td>⁴</td>
<td>Very Low Due to serious risk of bias and very serious imprecision ⁴ We are uncertain whether favipiravir increases or decreases respiratory failure or ARDS (total no of events = 8)</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation or ECMO</td>
<td><strong>Based on data from 19 patients in 1 studies.</strong></td>
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<td>-------------------------------</td>
<td>---------------------------------------------</td>
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<tr>
<td>Serious adverse events</td>
<td><strong>Critical</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>During treatment (14 days)</td>
<td><strong>During treatment (14 days)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Adverse events</td>
<td><strong>Important</strong></td>
<td></td>
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<tr>
<td>Clinical improvement</td>
<td><strong>Odds Ratio 1.25 (CI 95% 0.21 - 7.62)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>End of treatment (14 days)</td>
<td><strong>Based on data from 19 patients in 1 studies.</strong></td>
<td></td>
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<tr>
<td></td>
<td><strong>500</strong> per 1000</td>
<td><strong>555</strong> per 1000</td>
<td></td>
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<tr>
<td></td>
<td><strong>Difference: 56 more per 1000</strong> (CI 95% 326 fewer - 384 more)</td>
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<tr>
<td></td>
<td><strong>Very Low</strong></td>
<td></td>
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</tr>
<tr>
<td></td>
<td><strong>Due to serious risk of bias and very serious imprecision</strong></td>
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<tr>
<td></td>
<td><strong>We are uncertain whether favipiravir increases or decreases clinical improvement (total no of events = 10)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

1. **Systematic review** [41] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias:** **Serious. Imprecision:** **Very Serious.** Low number of patients, Only data from one study.
3. **Systematic review** [41] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias:** **Serious. Imprecision:** **Very Serious.** Low number of patients, Only data from one study.
5. **Systematic review** [41] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Systematic review** [41] with included studies: [43]. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Systematic review** [41] with included studies: [43]. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Systematic review** [41] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Risk of bias:** **Serious. Imprecision:** **Very Serious.** Low number of patients, Only data from one study.
5.4 - Lopinavir/ritonavir

**Strong Recommendation Against**

For people with COVID-19, only administer lopinavir/ritonavir in the context of randomised trials with appropriate ethical approval.

The Taskforce notes the release of the press statement from the chief investigators of the RECOVERY trial on 29 June that found no clinical benefit from using lopinavir-ritonavir in hospitalised patients with COVID-19. On 4 July WHO announced the lopinavir-ritonavir treatment arm of the Solidarity Trial had been discontinued with immediate effect. We await publication of the results of both trials.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

**Key Info**

**Benefits and harms**

In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include: gastrointestinal symptoms, hyperglycaemia, pancreatitis, lipid elevations, hepatic impairment, QT interval prolongation, and PR interval prolongation. Chronic harms include: increased risk of bleeding in patients with haemophilia, fat redistribution and immune reconstitution syndrome, among others. Lopinavir/ritonavir interacts with CYP3A and may result in increased plasma concentrations of the other drugs.

Harms associated with short-term use have been reported in three trials [26][27][12]. These include transient elevation of alanine aminotransferase and gastrointestinal symptoms, such as diarrhoea.

**Certainty of the Evidence**

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias and inconsistency, and very serious imprecision due to the low number of patients and/or the low number of observed events.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

**Equity**

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Because the benefit to harm ratio is uncertain, it is worth noting that this recommendation will protect more vulnerable populations, such as children.
Rationale

There is currently limited evidence about the impact of liponavir/ritonavir on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

In line with the ANZICS, ASID, AHPPC and IDSA recommendations [5][7][10][11], we therefore recommend that disease-modifying treatments should only be administered in the context of randomised trials with appropriate ethical approval.

Clinical Question/ PICO

| Population: | Patients with COVID-19 |
| Intervention: | Lopinavir/ritonavir |
| Comparator: | Standard care |

Summary

Evidence informing this recommendation comes from three randomised trials that compared lopinavir/ritonavir plus standard care to standard care alone in patients with COVID-19 [26][27][12]. One study included patients with severe illness [27], another included patients with mild/moderate illness [26] and the third included patients with moderate or severe illness [12].

Two studies provided data specific to mortality, respiratory failure or ARDS and requirement of mechanical ventilation or ECMO [26][27]. All studies provided data on adverse events and serious adverse events. Only one study reported data relating to clinical improvement at day 14 after treatment initiation [27].

Certainty of the evidence for each outcome is very low. This judgement is based on: serious risk of bias due to lack of personnel blinding and selective outcome reporting; serious imprecision due to the low number of patients and/or low number of observed events; and serious inconsistency in respiratory failure/ARDS, adverse events and serious adverse events, which may be related to the difference in illness severity between the studies.

According to the Therapeutic Goods Administration there are well-known side effects and harms associated with lopinavir/ritonavir. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include: gastrointestinal symptoms, hyperglycaemia, pancreatitis, lipid elevations, hepatic impairment, QT interval prolongation, and PR interval prolongation. Chronic harms include: increased risk of bleeding in patients with haemophilia, fat redistribution and immune reconstitution syndrome, among others. Lopinavir/ritonavir interacts with CYP3A and may result in increased plasma concentrations of the other drugs [10].

Based on the available evidence, there remains significant uncertainty whether lopinavir/ritonavir is more effective and safer than standard care in treating patients with COVID-19.
<table>
<thead>
<tr>
<th></th>
<th>Relative risk</th>
<th>(CI 95%)</th>
<th>Based on data from</th>
<th>Patients in studies</th>
<th>(Quality of evidence)</th>
<th>We are uncertain whether lopinavir/ritonavir increases or decreases mortality (total no of events = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
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<tr>
<td>End of treatment</td>
<td>Relative risk 0.77</td>
<td>(CI 95% 0.45 - 1.3)</td>
<td>Based on data from 250 patients in 2 studies.</td>
<td>214 per 1000</td>
<td>165 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
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<td></td>
<td>Difference: <strong>49 fewer</strong> per 1000</td>
<td>( CI 95% 118 fewer - 64 more )</td>
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</tr>
<tr>
<td><strong>Respiratory failure or ARDS</strong></td>
<td>Relative risk 0.59</td>
<td>(CI 95% 0.34 - 1.02)</td>
<td>Based on data from 225 patients in 2 studies.</td>
<td>233 per 1000</td>
<td>137 per 1000</td>
<td>Very Low Due to serious inconsistency and very serious imprecision</td>
</tr>
<tr>
<td>End of treatment</td>
<td></td>
<td></td>
<td></td>
<td>Difference: <strong>96 fewer</strong> per 1000</td>
<td>( CI 95% 154 fewer - 5 more )</td>
<td></td>
</tr>
<tr>
<td><strong>Mechanical ventilation or ECMO</strong></td>
<td>Relative risk 1.53</td>
<td>(CI 95% 0.49 - 4.76)</td>
<td>Based on data from 215 patients in 2 studies.</td>
<td>56 per 1000</td>
<td>86 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td>End of treatment</td>
<td></td>
<td></td>
<td></td>
<td>Difference: <strong>30 more</strong> per 1000</td>
<td>( CI 95% 29 fewer - 211 more )</td>
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</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>Relative risk 0.63</td>
<td>(CI 95% 0.39 - 1.02)</td>
<td>Based on data from 222 patients in 2 studies.</td>
<td>302 per 1000</td>
<td>190 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td>End of treatment</td>
<td></td>
<td></td>
<td></td>
<td>Difference: <strong>112 fewer</strong> per 1000</td>
<td>( CI 95% 184 fewer - 6 more )</td>
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<tr>
<td><strong>Adverse events</strong></td>
<td>Relative risk 1.39</td>
<td>(CI 95% 0.48 - 4.05)</td>
<td>Based on data from 287 patients in 3 studies.</td>
<td>358 per 1000</td>
<td>498 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td>End of treatment</td>
<td></td>
<td></td>
<td></td>
<td>Difference: <strong>140 more</strong> per 1000</td>
<td>( CI 95% 186 fewer - 1,092 more )</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical improvement</strong></td>
<td>Relative risk 1.52</td>
<td>(CI 95% 1.05 - 2.19)</td>
<td>Based on data from 241 patients in 2 studies.</td>
<td>305 per 1000</td>
<td>464 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td>Day 14 after treatment</td>
<td></td>
<td></td>
<td></td>
<td>Difference: <strong>159 more</strong> per 1000</td>
<td>( CI 95% 15 more - 363 more )</td>
<td></td>
</tr>
</tbody>
</table>

2. Risk of bias: Serious. Imprecision: Very Serious. Wide confidence intervals, Low number of patients.
4. Inconsistency: Serious. The direction of the effect is not consistent between the included studies. Imprecision: Very Serious.
5.5 - Remdesivir

5.5.1 - Remdesivir for adults

**Weak Recommendation**

Whenever possible remdesivir should be administered in the context of a randomised trial with appropriate ethical approval. Use of remdesivir for adults with moderate, severe or critical COVID-19 outside of a trial setting may be considered.

For information on dosages, length of treatment and characteristics of the patients in the trials used for this recommendation, see the Practical info tab below.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation.

**Practical Info**

**Treatment**

In the two trials where remdesivir was compared to placebo (Beigel 2020, Wang 2020), it was given as a daily intravenous infusion (200 mg initial dose, 100 mg maintenance) for 10 days. A third trial (Goldman 2020) compared a 10-day to a 5-day course of remdesivir but the magnitude of benefit remains uncertain for this treatment strategy. Given that the positive signal for benefit is only apparent in one trial with a 10-day course (Beigel 2020), we suggest considering this length of treatment until further evidence becomes available.

**Key inclusion criteria**

- > 18 years of age (Beigel 2020, Wang 2020), ≥ 12 years of age (Goldman 2020)
- Laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR)
- Clinical
  - Beigel 2020 [16]
    - Hospitalised with symptoms suggestive of COVID-19 AND one of the following criteria suggestive of lower respiratory tract infection:
- radiographic infiltrates by imaging study
- peripheral oxygen saturation (SpO2) ≤ 94% on room air
- requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

- Goldman 2020 [19]
  - radiographic infiltrates by imaging study
  - peripheral oxygen saturation (SpO2) ≤ 94% on room air or receiving supplemental oxygen

- Wang 2020 [40]
  - pneumonia confirmed by chest imaging AND
  - oxygen saturation of ≤ 94% on room air OR a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mm Hg

- Duration of symptoms
  - Beigel 2020: no limit to the duration of symptoms before enrolment
  - Wang 2020: within 12 days of symptom onset
  - Goldman 2020: not specified, confirmed SARS-CoV-2 (positive RT-PCR) within 4 days of randomisation

**Key exclusion criteria**
- Pregnancy or breastfeeding
- An alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range (Beigel 2020, Goldman 2020)
- Hepatic cirrhosis (Wang 2020 only)
- Impaired renal function (estimated glomerular filtration rate < 30 mL/min per 1.73 m²) or receipt of continuous renal replacement therapy, haemodialysis (Goldman 2020, Wang 2020) or peritoneal dialysis (Wang 2020).
- Allergy to study drug (Beigel 2020)
- Patients who were receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening (Goldman 2020)
- Patients with signs of multiorgan failure (Goldman 2020)
- Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against COVID-19 (Goldman 2020)

**Severity at baseline**

**Beigel 2020**

1063 patients

Baseline score on 8-category scale

1. Not hospitalised, no limitations of activities: n=0 (0%)
2. Not hospitalised, limitation of activities, home oxygen requirement, or both: n=0 (0%)
3. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control reasons): n=0 (0%)
4. Hospitalised, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19–related or otherwise): n=127 (12%)
5. Hospitalised, requiring supplemental oxygen: n=421 (40%)
6. Hospitalised, receiving noninvasive ventilation or high-flow oxygen devices: n=197 (19%)
7. Hospitalised, receiving invasive mechanical ventilation or ECMO: n=272 (26%)
8. Death: n=0 (0%)

Baseline score missing n=46 (4%)

**Wang 2020**

236 patients

Day 1 score on 6-category scale

1. Discharged or having reached discharge criteria (defined as clinical recovery—i.e. normalisation of pyrexia, respiratory rate < 24 breaths per minute, saturation of peripheral oxygen > 94% on room air, and relief of cough, all maintained for at least 72 hrs): n=0 (0%)
2. Hospital admission, not requiring supplemental oxygen: n=3 (1%)
3. Hospital admission, requiring supplemental oxygen: n=194 (82%)
4. Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation: n=37 (16%)
5. Hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation: n=1 (< 1%)
6. Death: n=1 (< 1%)

**Goldman 2020**
397 patients
Baseline score on a 7-category scale
1. Death: n=0 (0%) for both groups
2. Receiving invasive mechanical ventilation or ECMO: 5-day group n=4 (2%); 10-day group n=9 (5%)
3. Receiving noninvasive ventilation or high-flow oxygen: 5-day group n=49 (24%); 10-day group n=60 (30%)
4. Receiving low-flow supplemental oxygen: 5-day group n=113 (56%); 10-day group n=107 (54%)
5. Not receiving supplemental oxygen but requiring medical care: 5-day group n=34 (17%); 10-day group n=21 (11%)
6. Hospitalised, requiring neither supplemental oxygen nor ongoing medical care: n=0 (0%) for both groups
7. Not hospitalised: n=0 (0%) for both groups

Key Info

Benefits and harms

The two trials of remdesivir versus standard care provide preliminary evidence suggesting that remdesivir as a 10-day treatment has an acceptable safety profile. However, there remains uncertainty around the benefits and harms of remdesivir for patients with COVID-19. A third trial that compared a 10-day course to a 5-day course was too uncertain to inform decisions regarding length of treatment at this point.

Certainty of the Evidence

Certainty of the evidence for most reported outcomes is low or very low due to serious risk of bias and either serious imprecision or inconsistency in the direction of effect between studies. The exception is serious adverse events, which is considered to be of moderate certainty.

Preference and values

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients may prefer to wait while other patients may be more willing to opt for remdesivir.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. At this point, remdesivir remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

Equity

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Inequity may be further exacerbated in individuals who are eligible for treatment based on compassionate grounds due to factors that may limit access (such as geographic area).

Acceptability

Treatment is probably acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.

Feasibility

Remdesivir does not have regulatory approval in Australia but can be supplied after being exempted from the requirements of some parts of the Therapeutic Goods Act. The purpose of the exemption is to facilitate access and supply of remdesivir for the management of COVID-19 in the context of clinical trials and compassionate use. Implementation of the recommendation may be limited by the current arrangements for accessing remdesivir, in terms of the total number of doses available and factors that limit access to clinical trials more generally (such as geographic area).
Rationale
The effect of remdesivir on mortality is uncertain but it may decrease the time to recovery. Because of this the Taskforce gives a conditional recommendation for the use of remdesivir both within and outside the context of a randomised trial.

The populations in the three studies published to date approximate to the moderate, severe and critical illness categories outlined in these guidelines [16][19][40]. The studies had insufficient power to perform adequate subgroup analyses. Beigel 2020, however, reported small numerical differences between study arms in the outcomes of patients with critical COVID-19, but no statistically significant difference in the primary outcome (time to recovery) by baseline disease severity. The Taskforce recommendation to consider use of remdesivir outside of a randomised trial therefore applies to adult patients with moderate, severe or critical COVID-19.

Goldman 2020 compared a 5-day to a 10-day course of treatment, but since there is no established benefit for either approach yet, it remains uncertain that these results can inform the length of treatment.

Clinical Question/ PICO
Population: People with COVID-19
Intervention: Remdesivir
Comparator: Placebo

Summary
Evidence informing this recommendation comes from two randomised trials that compared remdesivir to placebo in patients with COVID-19 [16][40]. One study included 1063 patients with moderate to critical illness [16] and the other included 236 patients with severe to critical illness [40]. In both studies, randomisation was stratified by the level of disease severity, and in particular whether respiratory support was required.

Certainty of the evidence for most outcomes is low (all-cause mortality at day 14 and 28, respiratory failure or ARDS, time to recovery and adverse events) or very low (septic shock, clinical recovery and adverse events leading to discontinuation). The exception is serious adverse events, which is of moderate certainty. These judgements are based on lack of personnel blinding [16] (which is considered of no relevance in mortality) and either serious imprecision (due to low number of patients and/or observed events, reliance on a single study or wide confidence intervals) or inconsistency in the direction of effect between studies.

It is important to note that Beigel 2020 [16] provides preliminary results only and does not provide data for 28-day mortality. As such, this study will remain under surveillance and additional results will be included when they become available.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [14].

Based on the available evidence, it remains uncertain as to whether remdesivir is more effective and safer than placebo in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality (Day 14)</strong></td>
<td>Relative risk 0.71 (CI 95% 0.39 - 1.28) Based on data from 1,290 patients in 2 studies. ¹ (Randomized controlled)</td>
<td><strong>102</strong> per 1000 Remdesivir <strong>72</strong> per 1000 Placebo</td>
<td>Low Due to serious imprecision and inconsistency ²</td>
<td>Remdesivir may decrease all-cause mortality slightly (day 14; total no of events = 108)</td>
</tr>
<tr>
<td><strong>During treatment (14 days)</strong></td>
<td>Difference: <strong>30 fewer</strong> per 1000 ( CI 95% 62 fewer - 29 more )</td>
<td></td>
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</tr>
</tbody>
</table>
### Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>Number of Patients</th>
<th>Difference</th>
<th>Risk of Bias</th>
<th>Risk of Inconsistency</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality (Day 28)</strong></td>
<td>1.09 (0.54 - 2.18)</td>
<td>Based on data from 236 patients in 1 study.</td>
<td>128 per 1000</td>
<td>12 more per 1000</td>
<td>Low</td>
<td>Due to very serious imprecision</td>
<td>We are uncertain whether remdesivir increases or decreases all-cause mortality (day 28; total no of events = 32)</td>
</tr>
<tr>
<td><strong>Respiratory failure or ARDS</strong></td>
<td>0.84 (0.47 - 1.53)</td>
<td>Based on data from 1,296 patients in 2 studies.</td>
<td>117 per 1000</td>
<td>19 fewer per 1000</td>
<td>Low</td>
<td>Due to serious imprecision and inconsistency</td>
<td>We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (total no of events = 132)</td>
</tr>
<tr>
<td><strong>Septic shock</strong></td>
<td>1.02 (0.34 - 3.01)</td>
<td>Based on data from 1,296 patients in 2 studies.</td>
<td>10 per 1000</td>
<td>0 fewer per 1000</td>
<td>Very Low</td>
<td>Due to serious risk of bias, imprecision and inconsistency</td>
<td>We are uncertain whether remdesivir increases or decreases septic shock (total no of events = 13)</td>
</tr>
<tr>
<td><strong>Clinical recovery (Day 28)</strong></td>
<td>0.86 (0.46 - 1.64)</td>
<td>Based on data from 1,289 patients in 2 studies.</td>
<td>538 per 1000</td>
<td>75 fewer per 1000</td>
<td>Very Low</td>
<td>Due to serious risk of bias and very serious inconsistency</td>
<td>We are uncertain whether remdesivir improves or worsens clinical recovery (day 28)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>0.77 (0.63 - 0.94)</td>
<td>Based on data from 1,296 patients in 2 studies.</td>
<td>268 per 1000</td>
<td>62 fewer per 1000</td>
<td>Moderate</td>
<td>Due to serious risk of bias</td>
<td>Remdesivir probably decreases serious adverse events slightly (total no of events = 303)</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>0.94 (0.8 - 1.11)</td>
<td>Based on data from 1,296 patients in 2 studies.</td>
<td>370 per 1000</td>
<td>22 fewer per 1000</td>
<td>Low</td>
<td>Due to serious risk of bias and inconsistency</td>
<td>We are uncertain whether remdesivir increases or decreases adverse events</td>
</tr>
</tbody>
</table>

2. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Imprecision:** Serious. Wide confidence intervals.


4. **Imprecision:** Very Serious. Low number of patients. Only data from one study.


6. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Imprecision:** Serious. Wide confidence intervals.


8. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Imprecision:** Serious. Wide confidence intervals.


10. **Risk of bias:** Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Very 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., The direction of the effect is not consistent between the included studies.


<table>
<thead>
<tr>
<th>Adverse events leading to discontinuation During treatment (28 days)</th>
<th>Relative risk 1.29 (CI 95% 0.58 - 2.86) Based on data from 1,296 patients in 2 studies.</th>
<th>67 per 1000</th>
<th>86 per 1000</th>
<th>Very Low</th>
<th>Due to serious risk of bias, imprecision and inconsistency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Difference: <strong>19 more</strong> per 1000 ( CI 95% 28 fewer - 125 more )</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to recovery (Days)</th>
<th>Measured by: Rate ratio 1.32 (1.12 to 1.55) Based on data from: 607 patients in 1 studies. Follow up 28 days</th>
<th>15 days (Median)</th>
<th>11 days (Median)</th>
<th><strong>Low</strong></th>
<th>Due to serious risk of bias and imprecision</th>
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<tr>
<th>Time to improvement (Days)</th>
<th>Measured by: Hazard ratio 1.23 (0.87 to 1.75) Based on data from: 236 patients in 1 studies. Follow up 28 days</th>
<th>23 days (Median)</th>
<th>21 days (Median)</th>
<th><strong>Low</strong></th>
<th>Due to serious risk of bias and imprecision</th>
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<table>
<thead>
<tr>
<th>Important</th>
<th>Adverse events leading to discontinuation During treatment (28 days)</th>
<th>Relative risk 1.29 (CI 95% 0.58 - 2.86) Based on data from 1,296 patients in 2 studies.</th>
<th><strong>67</strong> per 1000</th>
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<tr>
<td></td>
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**Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce**
Clinical Question/ PICO

**Population:** Patients with severe COVID-19  
**Intervention:** Remdesivir 5-day treatment  
**Comparator:** Remdesivir 10-day treatment

**Summary**

Evidence informing this recommendation comes from a single randomised trial that compared 5-day to 10-day treatment with remdesivir in hospitalised patients with severe COVID-19. Patients were eligible if they were at least 12 years of age with PCR-confirmed SARS-CoV-2 infection before randomisation, had radiographic evidence of pulmonary infiltrates and oxygen saturation of 94% or less while breathing ambient air or were receiving supplemental oxygen.

The primary outcome was clinical status on day 14 using a 7-point scale (ranging from hospital discharge to death). Secondary outcomes included adverse events, serious adverse events (including acute respiratory failure/ARDS and septic shock), discontinuation of treatment due to adverse events and clinical recovery.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias (eligible patients were randomised using an interactive web response system; however no further details were provided and patients in the 10-day group had significantly worse clinical status than those in the 5-day group at enrolment; patients, personnel administering the intervention and outcome assessors were not blinded), and very serious imprecision (only one study with few patients and/or few events).

It is important to note that this publication only presents initial results from the first 400 patients in a trial that includes 6000 patients (NCT04292899). This analysis will be updated when results from the full cohort are available (the primary completion date of the trial is listed as June 2020).

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [14].
Based on the available evidence, it remains uncertain whether a 5-day treatment schedule of remdesivir is more effective and safer than a 10-day treatment schedule.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>14 days after commencing treatment</td>
<td>107 per 1000</td>
<td>80 per 1000</td>
<td>Very Low Due to very serious imprecision</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio 0.73 (CI 95% 0.37 - 1.44) Based on data from 397 patients in 1 studies.</td>
<td>Difference: 27 fewer per 1000 (CI 95% 65 fewer - 40 more)</td>
<td></td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases all-cause mortality (total no of events = 37)</td>
</tr>
<tr>
<td><strong>Acute respiratory failure or ARDS</strong></td>
<td>Up to 30 days following completion of treatment</td>
<td>117 per 1000</td>
<td>55 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio 0.44 (CI 95% 0.21 - 0.93) Based on data from 397 patients in 1 studies.</td>
<td>Difference: 62 fewer per 1000 (CI 95% 90 fewer - 7 fewer)</td>
<td></td>
<td>Remdesivir 5-day treatment may decrease acute respiratory failure or ARDS slightly (total no of events = 34)</td>
</tr>
<tr>
<td><strong>Septic shock</strong></td>
<td>Up to 30 days following completion of treatment</td>
<td>25 per 1000</td>
<td>9 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio 0.39 (CI 95% 0.07 - 2.02) Based on data from 397 patients in 1 studies.</td>
<td>Difference: 15 fewer per 1000 (CI 95% 23 fewer - 24 more)</td>
<td></td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (total no of events = 7)</td>
</tr>
<tr>
<td><strong>Clinical recovery</strong></td>
<td>14 days after commencing treatment</td>
<td>538 per 1000</td>
<td>644 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio 1.56 (CI 95% 1.04 - 2.33) Based on data from 397 patients in 1 studies.</td>
<td>Difference: 107 more per 1000 (CI 95% 10 more - 193 more)</td>
<td></td>
<td>Remdesivir 5-day treatment may improve clinical recovery slightly (total no of events = 235)</td>
</tr>
<tr>
<td><strong>Discharged from hospital</strong></td>
<td>14 days after commencing treatment</td>
<td>523 per 1000</td>
<td>600 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio 1.37 (CI 95% 0.92 - 2.04) Based on data from 397 patients in 1 studies.</td>
<td>Difference: 77 more per 1000 (CI 95% 21 fewer - 168 more)</td>
<td></td>
<td>We are uncertain whether remdesivir 5 day treatment increases or decreases number of patients discharged from hospital (total no of events = 223)</td>
</tr>
<tr>
<td>Event Type</td>
<td>Odds Ratio</td>
<td>CI 95%</td>
<td>Difference</td>
<td>CI 95%</td>
</tr>
<tr>
<td>------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>0.5</td>
<td>0.32 - 0.79</td>
<td>137 fewer</td>
<td>201 fewer - 51 fewer</td>
</tr>
<tr>
<td><strong>Very Low</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Up to 30 days following completion of treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events (Day 5)</strong></td>
<td>0.62</td>
<td>0.37 - 1.03</td>
<td>73 fewer</td>
<td>129 fewer - 5 more</td>
</tr>
<tr>
<td><strong>Very Low</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5 days after commencing treatment</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>0.86</td>
<td>0.55 - 1.33</td>
<td>30 fewer</td>
<td>131 fewer - 52 more</td>
</tr>
<tr>
<td><strong>Very Low</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Up to 30 days following completion of treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events (Day 5)</strong></td>
<td>0.92</td>
<td>0.62 - 1.38</td>
<td>20 fewer</td>
<td>117 fewer - 73 more</td>
</tr>
<tr>
<td><strong>Very Low</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5 days after commencing treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Discontinuation due to adverse events</strong></td>
<td>0.62</td>
<td>0.52 - 1.46</td>
<td>26 fewer</td>
<td>52 fewer - 29 more</td>
</tr>
<tr>
<td><strong>Very Low</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>During treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time to recovery</strong></td>
<td>0.81</td>
<td>0.64 to 1.04</td>
<td>11 (Median)</td>
<td>10 (Median)</td>
</tr>
<tr>
<td><strong>Very Low</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Days</strong></td>
<td></td>
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</tr>
</tbody>
</table>

2. **Imprecision: Very Serious.** Low number of patients, Only data from one study, due to low number of patients experiencing event.


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. **Imprecision: Very Serious.** Low number of patients, Only data from one study.


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. **Imprecision: Very Serious.** Low number of patients, Only data from one study.


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. **Imprecision: Very Serious.** Low number of patients, Only data from one study.


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. **Imprecision: Very Serious.** Low number of patients, Only data from one study.


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. **Imprecision: Very Serious.** Low number of patients, Only data from one study.


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. **Imprecision: Very Serious.** Low number of patients, Only data from one study.


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. **Imprecision: Very Serious.** Only data from one study, Low number of patients.


18. **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. **Imprecision: Very Serious.** Low number of patients, Only data from one study.

5.5.2 - Remdesivir for pregnant patients

Weak Recommendation Against

Use of remdesivir for pregnant patients with COVID-19 outside of a trial setting should not be considered routinely.

As pregnant patients are often excluded from clinical trials, use of remdesivir in this population would be outside a clinical trial setting. Pregnant patients receiving remdesivir should nonetheless be enrolled in national COVID-19 registries. Currently, there is no direct evidence of the effects of remdesivir in pregnant and breastfeeding patients. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation.

Practical Info

Treatment

In the two trials where remdesivir was compared to placebo (Beigel 2020, Wang 2020), it was given as a daily intravenous infusion (200 mg initial dose, 100 mg maintenance) for 10 days. A third trial (Goldman 2020) compared a 10-day to a 5-day course of remdesivir but the magnitude of benefit remains uncertain for this treatment strategy. Given that the positive signal for benefit is only apparent in one trial with a 10-day course (Beigel 2020), we suggest considering this length of treatment until further evidence becomes available.

Key inclusion criteria
- > 18 years of age (Beigel 2020, Wang 2020), > 12 years of age (Goldman 2020)
- laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR)
- Clinical
  - Beigel 2020 [16]
    - hospitalised with symptoms suggestive of COVID-19 AND one of the following criteria suggestive of lower respiratory tract infection:
      - radiographic infiltrates by imaging study
      - peripheral oxygen saturation (SpO2) ≤ 94% on room air
      - requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
  - Goldman 2020 [19]
    - radiographic infiltrates by imaging study
    - peripheral oxygen saturation (SpO2) ≤ 94% on room air or receiving supplemental oxygen
  - Wang 2020 [40]
    - pneumonia confirmed by chest imaging AND
    - oxygen saturation of ≤ 94% on room air OR a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mm Hg
- Duration of symptoms
  - Beigel 2020: no limit to the duration of symptoms before enrolment
Wang 2020: within 12 days of symptom onset
Goldman 2020: not specified, confirmed SARS-CoV-2 (positive RT-PCR) within 4 days of randomisation

Key exclusion criteria
- Pregnancy or breastfeeding
- An alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range (Beigel 2020, Goldman 2020)
- Hepatic cirrhosis (Wang 2020 only)
- Impaired renal function (estimated glomerular filtration rate < 30 mL/min per 1.73 m²) or receipt of continuous renal replacement therapy, haemodialysis (Goldman 2020, Wang 2020) or peritoneal dialysis (Wang 2020).
- Allergy to study drug (Beigel 2020)
- Patients who were receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening (Goldman 2020)
- Patients with signs of multiorgan failure (Goldman 2020)
- Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against COVID-19 (Goldman 2020)

Severity at baseline

Beigel 2020
1063 patients
Baseline score on 8-category scale
1. Not hospitalised, no limitations of activities: n=0 (0%)
2. Not hospitalised, limitation of activities, home oxygen requirement, or both: n=0 (0%)
3. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control reasons): n=0 (0%)
4. Hospitalised, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19–related or otherwise): n=127 (12%)
5. Hospitalised, requiring supplemental oxygen: n=421 (40%)
6. Hospitalised, receiving noninvasive ventilation or high-flow oxygen devices: n=197 (19%)
7. Hospitalised, receiving invasive mechanical ventilation or ECMO: n=272 (26%)
8. Death: n=0 (0%)
Baseline score missing n=46 (4%)

Wang 2020
236 patients
Day 1 score on 6-category scale
1. Discharged or having reached discharge criteria (defined as clinical recovery—i.e. normalisation of pyrexia, respiratory rate < 24 breaths per minute, saturation of peripheral oxygen > 94% on room air, and relief of cough, all maintained for at least 72 hrs): n=0 (0%)
2. Hospital admission, not requiring supplemental oxygen: n=3 (1%)
3. Hospital admission, requiring supplemental oxygen: n=194 (82%)
4. Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation: n=37 (16%)
5. Hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation: n=1 (< 1%)
6. Death: n=1 (< 1%)

Goldman 2020
397 patients
Baseline score on a 7-category scale
1. Death: n=0 (0%) for both groups
2. Receiving invasive mechanical ventilation or ECMO: 5-day group n=4 (2%); 10-day group n=9 (5%)
3. Receiving noninvasive ventilation or high-flow oxygen: 5-day group n=49 (24%); 10-day group n=60 (30%)
4. Receiving low-flow supplemental oxygen: 5-day group n=113 (56%); 10-day group n=107 (54%)
5. Not receiving supplemental oxygen but requiring medical care: 5-day group n=34 (17%); 10-day group n=21 (11%)
6. Hospitalised, requiring neither supplemental oxygen nor ongoing medical care: n=0 (0%) for both groups
7. Not hospitalised: n=0 (0%) for both groups

Key Info

Benefits and harms
There remains uncertainty around the benefits and harms of remdesivir for pregnant patients with COVID-19. Evidence from a trial comparing a 10-day to a 5-day course was too uncertain to inform decisions regarding length of treatment at this point.

Certainty of the Evidence
Very Low
Certainty of the evidence for most reported outcomes is very low due to serious risk of bias, indirectness and either serious imprecision or inconsistency in the direction of effect between studies. The exception is serious adverse events, which is considered to be of low certainty.

**Preference and values**

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding patients at this point. Since there is uncertainty regarding the benefit to harm ratio for patients and their babies, the panel believes some patients might prefer to wait while others might be more willing to opt for treatment.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. At this point, remdesivir remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

**Equity**

There is a risk of creating inequity as pregnant patients are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Inequity may be further exacerbated in individuals who are eligible for treatment based on compassionate grounds due to factors that may limit access (such as geographic area).

**Acceptability**

We have no systematically collected evidence regarding acceptability by pregnant and breastfeeding patients.

**Feasibility**

Remdesivir does not have regulatory approval in Australia but can be supplied after being exempted from the requirements of some parts of the Therapeutic Goods Act. The purpose of the exemption is to facilitate access and supply of remdesivir for the management of COVID-19 in the context of clinical trials and compassionate use. Implementation of the recommendation may be limited by the current arrangements for accessing remdesivir, in terms of the total number of doses available and factors that limit access to clinical trials more generally (such as geographic area).

**Rationale**

There is currently no direct evidence about the impact of remdesivir on outcomes relevant to pregnant and breastfeeding patients with COVID-19 and insufficient data on safety. The effect of remdesivir on mortality is uncertain but it may decrease the time to recovery in non-pregnant adults.

The severity of disease is an important factor when considering the use of remdesivir. For pregnant patients with severe or critical COVID-19, the harm to benefit ratio may differ compared to pregnant patients with mild or moderate illness. The populations in the three studies published to date approximate to the moderate, severe and critical illness categories outlined in these guidelines [16][19][40]. The studies had insufficient power to perform adequate subgroup analyses. Beigel 2020, however, reported small numerical differences between study arms in the outcomes of patients with critical COVID-19, but no statistically significant difference in the primary outcome (time to recovery) by baseline disease severity. Goldman 2020 compared 5-day to a 10-day course of treatment, but since there is no established benefit for either approach yet, it remains uncertain that their results could inform the length of treatment at this point.

**Clinical Question/ PICO**

| Population: | Pregnant patients with COVID-19 [adapted from general adult population] |
Summary
Evidence informing this recommendation comes from two randomised trials that compared remdesivir to placebo in adult patients with COVID-19; neither trial included pregnant or breastfeeding patients. One study included 1063 patients with moderate to critical illness [16] and the other included 236 patients with severe to critical illness [40]. The evidence is judged to be applicable to pregnant and breastfeeding patients.

In both studies, randomisation was stratified by the level of disease severity, and in particular whether respiratory support was required. Patients were 18 years of age or older and both studies excluded pregnant and breastfeeding patients. The mean age of patients receiving remdesivir ranged from 58 to 66 years, with the proportion of women ranging from 35% to 44%. The mean age of those receiving standard care ranged from 59 to 64 years, with the proportion of women ranging from 35% to 36%.

Certainty of the evidence for the majority of outcomes is very low. The exception is serious adverse events, which is considered to be of low certainty. These judgements are based on lack of personnel blinding [16] (which is considered of no relevance in mortality), serious imprecision (due to low number of patients and/or observed events, reliance on a single study or wide confidence intervals) or inconsistency in the direction of effect between studies, and indirectness (due to the absence of pregnant or breastfeeding patients in included studies).

It is important to note that Beigel 2020 [16] provides preliminary results only and does not provide data for 28-day mortality. As such, this study will remain under surveillance and additional results will be included when they become available.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [14]. There is currently insufficient evidence to assess adverse outcomes following treatment with remdesivir in pregnant and breastfeeding patients.

Based on the available evidence, it remains uncertain as to whether remdesivir is more effective and safer than placebo in treating pregnant patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (Day 14)</td>
<td>Relative risk 0.71 (CI 95% 0.39 - 1.28) Based on data from 1,290 patients in 2 studies. 1 (Randomized controlled)</td>
<td>102 per 1000 72 per 1000</td>
<td>Very Low Due to serious imprecision, inconsistency and indirectness 2</td>
<td>We are uncertain whether remdesivir increases or decreases all-cause mortality (day 14; total no of events = 108)</td>
</tr>
<tr>
<td>During treatment (14 days)</td>
<td>Difference: 30 fewer per 1000 ( CI 95% 62 fewer - 29 more )</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>9 Critical</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All-cause mortality (Day 28)</td>
<td>Relative risk 1.09 (CI 95% 0.54 - 2.18) Based on data from 236 patients in 1 studies. 3 (Randomized controlled)</td>
<td>128 per 1000 140 per 1000</td>
<td>Very Low Due to very serious imprecision and serious indirectness 4</td>
<td>We are uncertain whether remdesivir increases or decreases all-cause mortality (day 28; total no of events = 32)</td>
</tr>
<tr>
<td>During treatment (28 days)</td>
<td>Difference: 12 more per 1000 ( CI 95% 59 fewer - 151 more )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event Description</td>
<td>Relative Risk</td>
<td>CI 95%</td>
<td>Difference</td>
<td>Risk of Bias and Inconsistency</td>
</tr>
<tr>
<td>-------------------</td>
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</tr>
<tr>
<td><strong>Critical Respiratory failure or ARDS</strong>&lt;br&gt;(During treatment)</td>
<td>0.84</td>
<td>0.47 - 1.53</td>
<td>19 fewer per 1000</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Septic shock</strong>&lt;br&gt;(During treatment)</td>
<td>1.02</td>
<td>0.34 - 3.01</td>
<td>0 fewer per 1000</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Clinical recovery (Day 28)</strong>&lt;br&gt;(During treatment)</td>
<td>0.86</td>
<td>0.46 - 1.64</td>
<td>75 fewer per 1000</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong>&lt;br&gt;(Number of patients experiencing one or more serious adverse events)</td>
<td>0.77</td>
<td>0.63 - 0.94</td>
<td>62 fewer per 1000</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Adverse events</strong>&lt;br&gt;(Number of patients experiencing one or more adverse events)</td>
<td>0.94</td>
<td>0.8 - 1.11</td>
<td>22 fewer per 1000</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Adverse events leading to discontinuation</strong>&lt;br&gt;(During treatment)</td>
<td>1.29</td>
<td>0.58 - 2.86</td>
<td>19 more per 1000</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

2. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Wide confidence intervals.


4. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


6. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Wide confidence intervals.


8. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Wide confidence intervals.


10. **Risk of bias:** Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Very 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., The direction of the effect is not consistent between the included studies.


12. **Risk of bias:** Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness:** Serious. Differences between the population of interest and those studied.


14. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias,

<table>
<thead>
<tr>
<th>Time to recovery (Days)</th>
<th>Measured by: Rate ratio 1.32 (1.12 to 1.55)</th>
<th>Based on data from: 607 patients in 1 studies. (Randomized controlled) Follow up 28 days</th>
<th>15 days (Median)</th>
<th>11 days (Median)</th>
<th>Very Low Due to serious risk of bias, imprecision and indirectness 17</th>
<th>We are uncertain whether remdesivir affects time to recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to improvement (Days)</td>
<td>Measured by: Hazard ratio 1.23 (0.87 to 1.75)</td>
<td>Based on data from: 236 patients in 1 studies. (Randomized controlled) Follow up 28 days</td>
<td>23 days (Median)</td>
<td>21 days (Median)</td>
<td>Very Low Due to serious risk of bias, imprecision and indirectness 19</td>
<td>We are uncertain whether remdesivir affects time to improvement</td>
</tr>
</tbody>
</table>

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**Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce**
Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the population of interest and those studied.


16. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.

17. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.

18. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.

**Clinical Question/ PICO**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong></td>
<td>Pregnant patients with severe COVID-19 [adapted from general adult population]</td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
<td>Remdesivir 5-day treatment</td>
</tr>
<tr>
<td><strong>Comparator:</strong></td>
<td>Remdesivir 10-day treatment</td>
</tr>
</tbody>
</table>

**Summary**

Evidence informing this recommendation comes from a single randomised trial that compared 5-day to 10-day treatment with remdesivir in hospitalised patients with severe COVID-19; the trial did not include pregnant patients. Patients were eligible if they were at least 12 years of age with PCR-confirmed SARS-CoV-2 infection before randomisation, had radiographic evidence of pulmonary infiltrates and oxygen saturation of 94% or less while breathing ambient air or were receiving supplemental oxygen. The evidence is judged to be applicable to pregnant patients.

The primary outcome was clinical status on day 14 using a 7-point scale (ranging from hospital discharge to death). Secondary outcomes included adverse events, serious adverse events (including acute respiratory failure/ARDS and septic shock), discontinuation of treatment due to adverse events and clinical recovery.

Certainty of the evidence for all reported outcomes is very low. This judgement is based on serious risk of bias (eligible patients were randomised using an interactive web response system; however no further details were provided and patients in the 10-day group had significantly worse clinical status than those in the 5-day group at enrolment; patients, personnel administering the intervention and outcome assessors were not blinded), very serious imprecision (only one study with few patients and/or few events) and serious indirectness (population included adults who were not pregnant).

It is important to note that this publication only presents initial results from the first 400 patients in a trial that includes 6000 patients (NCT04292899). This analysis will be updated when results from the full cohort are available (the primary completion date of the trial is listed as June 2020).

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [14].

Based on the available evidence, it remains uncertain whether a 5-day treatment schedule of remdesivir is more effective and safer than a 10-day treatment schedule.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>14 days after commencing treatment</td>
<td>Odds Ratio 0.73 (CI 95% 0.37 - 1.44) Based on data from 397 patients in 1 studies.¹</td>
<td>107 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases all-cause mortality (total no of events = 37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td>80 per 1000</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Difference: 27 fewer per 1000 ( CI 95% 65 fewer - 40 more )</td>
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<tr>
<td></td>
<td></td>
<td>9 Critical</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acute respiratory failure or ARDS</td>
<td>Up to 30 days following completion of treatment</td>
<td>Odds Ratio 0.44 (CI 95% 0.21 - 0.93) Based on data from 397 patients in 1 studies.³</td>
<td>117 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases acute respiratory failure or ARDS (total no of events = 34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td>55 per 1000</td>
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<tr>
<td></td>
<td></td>
<td>Difference: 62 fewer per 1000 ( CI 95% 90 fewer - 7 fewer )</td>
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<tr>
<td></td>
<td></td>
<td>9 Critical</td>
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</tr>
<tr>
<td>Septic shock</td>
<td>Up to 30 days following completion of treatment</td>
<td>Odds Ratio 0.39 (CI 95% 0.07 - 2.02) Based on data from 397 patients in 1 studies.⁵</td>
<td>25 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (total no of events = 7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td>9 per 1000</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Difference: 15 fewer per 1000 ( CI 95% 23 fewer - 24 more )</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 Critical</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>14 days after commencing treatment</td>
<td>Odds Ratio 1.56 (CI 95% 1.04 - 2.33) Based on data from 397 patients in 1 studies.⁷</td>
<td>538 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases clinical recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td>644 per 1000</td>
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<tr>
<td></td>
<td></td>
<td>Difference: 107 more per 1000 ( CI 95% 10 more - 193 more )</td>
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<td></td>
<td></td>
<td>6 Important</td>
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</tr>
<tr>
<td>Discharged from hospital</td>
<td>14 days after commencing treatment</td>
<td>Odds Ratio 1.37 (CI 95% 0.92 - 2.04) Based on data from 397 patients in 1 studies.⁹</td>
<td>523 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases number of patients discharged from hospital (total no of events = 223)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td>600 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 77 more per 1000 ( CI 95% 21 more - 168 more )</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>6 Important</td>
<td></td>
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</tr>
<tr>
<td>Serious adverse events</td>
<td>Up to 30 days</td>
<td>Odds Ratio 0.5 (CI 95% 0.32 - 0.79) Based on data from 397 patients</td>
<td>345 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment slightly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td>208 per 1000</td>
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</tr>
</tbody>
</table>

¹ Based on data from 397 patients in 1 studies.
² Based on data from 397 patients in 1 studies.
³ Based on data from 397 patients in 1 studies.
⁴ Based on data from 397 patients in 1 studies.
⁵ Based on data from 397 patients in 1 studies.
⁶ Based on data from 397 patients in 1 studies.
⁷ Based on data from 397 patients in 1 studies.
⁸ Based on data from 397 patients in 1 studies.
⁹ Based on data from 397 patients in 1 studies.
¹⁰ Based on data from 397 patients in 1 studies.

2. **Imprecision:** Very Serious. Low number of patients. Only data from one study, due to low number of patients experiencing event.

### Serious adverse events (Day 5)
5 days after commencing treatment

- **Patients in 1 studies.[11] (Randomized controlled)**
- **Odds Ratio 0.62 (CI 95% 0.37 - 1.03)** Based on data from 397 patients in 1 studies.[11] (Randomized controlled)

**Difference:** 228 fewer per 1000 (CI 95% 201 fewer - 51 fewer)

**Very Low** Due to serious risk of bias and very serious imprecision.

We are uncertain whether remdesivir 5-day treatment increases or decreases serious adverse events at day 5 (total no of events = 76).

### Adverse events
Up to 30 days following completion of treatment

- **Odds Ratio 0.86 (CI 95% 0.55 - 1.33)** Based on data from 397 patients in 1 studies.[15] (Randomized controlled)

**Difference:** 736 fewer per 1000 (CI 95% 131 fewer - 52 more)

**Very Low** Due to serious risk of bias and very serious imprecision.

We are uncertain whether remdesivir 5-day treatment increases or decreases adverse events (total no of events = 286).

### Adverse events (Day 5)
5 days after commencing treatment

- **Odds Ratio 0.92 (CI 95% 0.62 - 1.38)** Based on data from 397 patients in 1 studies.[17] (Randomized controlled)

**Difference:** 619 fewer per 1000 (CI 95% 117 fewer - 73 more)

**Very Low** Due to serious risk of bias and very serious imprecision.

We are uncertain whether remdesivir 5-day treatment increases or decreases adverse events at day 5 (total no of events = 242).

### Discontinuation due to adverse events
During treatment

- **Odds Ratio 0.62 (CI 95% 0.26 - 1.46)** Based on data from 397 patients in 1 studies.[19] (Randomized controlled)

**Difference:** 71 fewer per 1000 (CI 95% 52 fewer - 29 more)

**Very Low** Due to serious risk of bias and very serious imprecision.

We are uncertain whether remdesivir 5-day treatment increases or decreases number of patients who discontinue treatment due to adverse events (total no of events = 29).

### Time to recovery
Days

- **Measured by: Hazard ratio: 0.81 (0.64 to 1.04)** Lower better (Randomized controlled)
  - **Median:** 11 (CI 95%)
  - **Median:** 10 (CI 95%)

**Very Low** Due to serious risk of bias and very serious imprecision.

We are uncertain whether remdesivir 5-day treatment increases or decreases time to recovery.

4. **Risk of bias:** Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


6. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


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. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


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. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to [reason].


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. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to [reason].


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. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to [reason].


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. **Imprecision:** Very Serious. Only data from one study, Low number of patients, due to [reason].


18. **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. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to [reason].


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. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to [reason].

21. **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. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to [reason].
5.5.3 - Remdesivir for children or adolescents

**Weak Recommendation Against**

Use of remdesivir for children or adolescents with COVID-19 outside of a trial setting should not be considered routinely.

*If treatment is considered—in exceptional circumstances—it should be in consultation with a clinical reference group, such as the ANZPID COVID-19 Clinical Reference Group. Informed consent from parents/caregivers should also be obtained. Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab.*

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation.

**Practical Info**

**Treatment**

Use of remdesivir in children or adolescents with COVID-19 should be considered in consultation with an appropriate clinical reference group. The Australasian Society for Infectious Diseases (ASID) paediatric special interest group (ANZPID) has formed a clinical reference group to advise paediatric infection specialists on therapy for children with COVID-19. The ANZPID COVID-19 Clinical Reference Group can be urgently convened to discuss individual patient management and provide a recommendation to the treating team on the use of a disease-modifying treatment when needed. Informed consent from parents/caregivers should also be obtained.

In the two trials where remdesivir was compared to placebo (Beigel 2020, Wang 2020), it was given as a daily intravenous infusion (200 mg initial dose, 100 mg maintenance) for 10 days in adults. A third trial (Goldman 2020) compared a 10-day to a 5-day course of remdesivir in adults but the magnitude of benefit remains uncertain for this treatment strategy. Given that the positive signal for benefit is only apparent in one trial with a 10-day course (Beigel 2020), we suggest considering this length of treatment, until further evidence becomes available.

**Key inclusion criteria**

- > 18 years of age (Beigel 2020, Wang 2020), > 12 years of age (Goldman 2020)
- Laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR)
- **Clinical**
  - Beigel 2020 [16]
    - hospitalised with symptoms suggestive of COVID-19 AND one of the following criteria suggestive of lower respiratory tract infection:
      - radiographic infiltrates by imaging study
      - peripheral oxygen saturation (SpO2) ≤ 94% on room air
      - requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
  - Goldman 2020 [19]
    - radiographic infiltrates by imaging study
    - peripheral oxygen saturation (SpO2) ≤ 94% on room air or receiving supplemental oxygen
  - Wang 2020 [40]
    - pneumonia confirmed by chest imaging AND
    - oxygen saturation of ≤ 94% on room air OR a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mm Hg
- Duration of symptoms
  - Beigel 2020: no limit to the duration of symptoms before enrolment
  - Wang 2020: within 12 days of symptom onset
  - Goldman 2020: not specified, confirmed SARS-CoV-2 (positive RT-PCR) within 4 days of randomisation

**Key exclusion criteria**

- Pregnancy or breastfeeding
- An alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range (Beigel 2020, Goldman 2020)
- Hepatic cirrhosis (Wang 2020 only)
• Impaired renal function (estimated glomerular filtration rate < 30 mL/min per 1·73 m²) or receipt of continuous renal replacement therapy, haemodialysis (Goldman 2020, Wang 2020) or peritoneal dialysis (Wang 2020).
• Allergy to study drug (Beigel 2020)
• Patients who were receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening (Goldman 2020)
• Patients with signs of multiorgan failure (Goldman 2020)
• Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against COVID-19 (Goldman 2020)

Severity at baseline
Beigel 2020
1063 patients
Baseline score on 8-category scale
1. Not hospitalised, no limitations of activities: n=0 (0%)
2. Not hospitalised, limitation of activities, home oxygen requirement, or both: n=0 (0%)
3. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control reasons): n=0 (0%)
4. Hospitalised, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19–related or otherwise): n=127 (12%)
5. Hospitalised, requiring supplemental oxygen: n=421 (40%)
6. Hospitalised, receiving noninvasive ventilation or high-flow oxygen devices: n=197 (19%)
7. Hospitalised, receiving invasive mechanical ventilation or ECMO: n=272 (26%)
8. Death: n=0 (0%)
Baseline score missing n=46 (4%)

Wang 2020
236 patients
Day 1 score on 6-category scale
1. Discharged or having reached discharge criteria (defined as clinical recovery—i.e. normalisation of pyrexia, respiratory rate < 24 breaths per minute, saturation of peripheral oxygen > 94% on room air, and relief of cough, all maintained for at least 72 hrs): n=0 (0%)
2. Hospital admission, not requiring supplemental oxygen: n=3 (1%)
3. Hospital admission, requiring supplemental oxygen: n=194 (82%)
4. Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation: n=37 (16%)
5. Hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation: n=1 (< 1%)
6. Death: n=1 (< 1%)

Goldman 2020
397 patients
Baseline score on a 7-category scale
1. Death: n=0 (0%) for both groups
2. Receiving invasive mechanical ventilation or ECMO: 5-day group n=4 (2%); 10-day group n=9 (5%)
3. Receiving noninvasive ventilation or high-flow oxygen: 5-day group n=49 (24%); 10-day group n=60 (30%)
4. Receiving low-flow supplemental oxygen: 5-day group n=113 (56%); 10-day group n=107 (54%)
5. Not receiving supplemental oxygen but requiring medical care: 5-day group n=34 (17%); 10-day group n=21 (11%)
6. Hospitalised, requiring neither supplemental oxygen nor ongoing medical care: n=0 (0%) for both groups
7. Not hospitalised: n=0 (0%) for both groups

Key Info

The two trials of remdesivir versus standard care provide preliminary evidence suggesting that remdesivir as a 10-day treatment has an acceptable safety profile. A third trial that compared a 10-day course to a 5-day course was too uncertain to inform decisions regarding length of treatment at this point. The results are based on adults (aged 44 to 75 years)—the trials did not include children and adolescents. There remains uncertainty around the benefits and harms of remdesivir for children and adolescents with COVID-19.

Certainty of the Evidence
Very Low
Certainty of the evidence for most reported outcomes is very low due to serious risk of bias, indirectness and either serious imprecision or inconsistency in the direction of effect between studies. The exception is serious adverse events, which is considered to be of low certainty.

**Preference and values**

We have no systematically collected information regarding the preferences and values of patients or of their parents/caregivers. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers) may prefer to wait, while others may be more willing to take risks.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. At this point, remdesivir remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

**Equity**

There is a risk of creating inequity as some populations, including most children, are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Inequity may be further exacerbated in individuals who are eligible for treatment based on compassionate grounds due to factors that may limit access (such as geographic area).

**Acceptability**

We have no systematically collected evidence regarding acceptability. However, obtaining and maintaining intravenous access in children may be more difficult than in adults and may therefore affect acceptability.

**Feasibility**

Remdesivir does not have regulatory approval in Australia but can be supplied after being exempted from the requirements of some parts of the Therapeutic Goods Act. The purpose of the exemption is to facilitate access and supply of remdesivir for the management of COVID-19 in the context of clinical trials and compassionate use. Implementation of the recommendation may be limited by the current arrangements for accessing remdesivir, in terms of the total number of doses available and factors that limit access to clinical trials more generally (such as geographic area).

**Rationale**

The effect of remdesivir on mortality is uncertain but it may decrease the time to recovery and the risk of serious adverse events in adults. Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Because of this the Taskforce gives a conditional recommendation against the use of remdesivir outside the context of a randomised trial for children and adolescents.

The populations in the three studies published to date (adults aged 44-75 years) approximate to the moderate, severe and critical illness categories outlined in this guideline. The studies had insufficient power to perform adequate subgroup analyses. Beigel 2020, however, reported small numerical differences between study arms in the outcomes of patients with critical COVID-19, but no statistically significant difference in the primary outcome (time to recovery) by baseline disease severity. Goldman 2020 compared a 5-day to a 10-day course of treatment, but since there is no established benefit for either approach yet, it remains uncertain that these results can inform the length of treatment.

**Clinical Question/ PICO**

**Population:** Children and adolescents with COVID-19 [adapted from general adult population]
**Intervention:** Remdesivir  
**Comparator:** Placebo

**Summary**

Evidence informing this recommendation comes from two randomised trials that compared remdesivir to placebo in adult patients with COVID-19; neither trial included children or adolescents. One study included 1063 patients with moderate to critical illness [14] and the other included 236 patients with severe to critical illness [31]. In both studies, randomisation was stratified by the level of disease severity, and in particular whether respiratory support was required. In both studies, patients had to be 18 years of age or older to be included (mean age ranged from 59 to 66 years in the remdesivir group and 59 to 64 years in the control group). The evidence is judged to be applicable to children and adolescents.

Certainty of the evidence for the majority of outcomes is very low. The exception is serious adverse events, which is considered to be of low certainty. These judgements are based on lack of personnel blinding (which is considered of no relevance in mortality) and either serious imprecision (due to low number of patients and/or observed events, reliance on a single study or wide confidence intervals) or inconsistency in the direction of effect between studies. All outcomes were downgraded for indirectness as results were based on adults.

It is important to note that Beigel 2020 [16] provides preliminary results only and does not provide data for 28-day mortality. As such, this study will remain under surveillance and additional results will be included when they become available.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [14]. There is currently insufficient evidence to assess adverse outcomes following treatment with remdesivir in children or adolescents.

Based on the available evidence, it remains uncertain as to whether remdesivir is more effective and safer than placebo in treating children or adolescents with COVID-19.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates Placebo</th>
<th>Remdesivir</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (Day 14)</td>
<td>Relative risk 0.71 (CI 95% 0.39 - 1.28) Based on data from 1,290 patients in 2 studies. 1 (Randomized controlled)</td>
<td><strong>102</strong> per 1000 <strong>72</strong> per 1000</td>
<td><strong>Very Low</strong> Due to serious imprecision, inconsistency and indirectness 2</td>
<td>We are uncertain whether remdesivir increases or decreases all-cause mortality (day 14; total no of events = 108)</td>
<td></td>
</tr>
<tr>
<td>During treatment (14 days)</td>
<td>9 Critical</td>
<td>Difference: <strong>30 fewer</strong> per 1000 (CI 95% 62 fewer - 29 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality (Day 28)</td>
<td>Relative risk 1.09 (CI 95% 0.54 - 2.18) Based on data from 236 patients in 1 studies. 3 (Randomized controlled)</td>
<td><strong>128</strong> per 1000 <strong>140</strong> per 1000</td>
<td><strong>Very Low</strong> Due to very serious imprecision and serious indirectness 4</td>
<td>We are uncertain whether remdesivir increases or decreases all-cause mortality (day 28; total no of events = 32)</td>
<td></td>
</tr>
<tr>
<td>During treatment (28 days)</td>
<td>9 Critical</td>
<td>Difference: <strong>12 more</strong> per 1000 (CI 95% 59 fewer - 151 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Respiratory failure or ARDS**  
During treatment (28 days) | Relative risk 0.84  
(CI 95% 0.47 - 1.53)  
Based on data from 1,296 patients in 2 studies.  
(Randomized controlled) | 117 per 1000 | 98 per 1000 | Very Low  
Due to serious imprecision, inconsistency and indirectness  
(We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (total no of events = 132)) |
|-----------------------------|-------------------------------------------------|----------------|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Septic shock**  
During treatment (28 days) | Relative risk 1.02  
(CI 95% 0.34 - 3.01)  
Based on data from 1,296 patients in 2 studies.  
(Randomized controlled) | 10 per 1000 | 10 per 1000 | Very Low  
Due to serious risk of bias, imprecision, inconsistency and indirectness  
(We are uncertain whether remdesivir increases or decreases septic shock (total no of events = 13)) |
| **Clinical recovery**  
(Day 28)  
During treatment (28 days) | Relative risk 0.86  
(CI 95% 0.46 - 1.64)  
Based on data from 1,289 patients in 2 studies.  
(Randomized controlled) | 538 per 1000 | 463 per 1000 | Very Low  
Due to serious risk of bias and very serious inconsistency  
(We are uncertain whether remdesivir improves or worsens clinical recovery (Day 28)) |
| **Serious adverse events**  
Number of patients experiencing one or more serious adverse events | Relative risk 0.77  
(CI 95% 0.63 - 0.94)  
Based on data from 1,296 patients in 2 studies.  
(Randomized controlled) | 268 per 1000 | 206 per 1000 | Low  
Due to serious risk of bias and indirectness  
(Remdesivir probably decreases serious adverse events slightly (total no of events = 303)) |
| **Adverse events**  
Number of patients experiencing one or more adverse events | Relative risk 0.94  
(CI 95% 0.8 - 1.11)  
Based on data from 1,296 patients in 2 studies.  
(Randomized controlled) | 370 per 1000 | 348 per 1000 | Very Low  
Due to serious risk of bias, inconsistency and indirectness  
(We are uncertain whether remdesivir increases or decreases adverse events) |
| **Adverse events leading to discontinuation**  
During treatment (28 days) | Relative risk 1.29  
(CI 95% 0.58 - 2.86)  
Based on data from 1,296 patients in 2 studies.  
(Randomized controlled) | 67 per 1000 | 86 per 1000 | Very Low  
Due to serious risk of bias, imprecision, inconsistency and indirectness  
(We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation) |

2. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Wide confidence intervals.


4. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Very Serious. Low number of patients. Only data from one study.


6. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Wide confidence intervals.


8. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Wide confidence intervals.


10. **Risk of bias:** Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Very 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,. The direction of the effect is not consistent between the included studies.


12. **Risk of bias:** Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness:** Serious. Differences between the population of interest and those studied.


14. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. Differences between the population of interest and those studied.

16. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.

17. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.

18. **Primary study[40].** **Baseline/comparator:** Control arm of reference used for intervention.

19. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.

### Clinical Question/ PICO

**Population:** Children and adolescents with severe COVID-19 [adapted from general adult population]

**Intervention:** Remdesivir 5-day treatment

**Comparator:** Remdesivir 10-day treatment

**Summary**

Evidence informing this recommendation comes from a single randomised trial that compared 5-day to 10-day treatment with remdesivir in hospitalised patients with severe COVID-19; the trial did not include children or adolescents. Patients were eligible if they were at least 12 years of age with PCR-confirmed SARS-CoV-2 infection before randomisation, had radiographic evidence of pulmonary infiltrates and oxygen saturation of 94% or less while breathing ambient air or were receiving supplemental oxygen. The median age reported in the trial was 61 years [IQR 50-69] for the 5-day group and 62 years [IQR 50-71] for the 10-day group. The evidence is judged to be applicable to children and adolescents.

The primary outcome was clinical status on day 14 using a 7-point scale (ranging from hospital discharge to death). Secondary outcomes included adverse events, serious adverse events (including acute respiratory failure/ARDS and septic shock), discontinuation of treatment due to adverse events and clinical recovery.

Certainty of the evidence for all reported outcomes is very low. This judgement is based on serious risk of bias (eligible patients were randomised using an interactive web response system; however no further details were provided and patients in the 10-day group had significantly worse clinical status than those in the 5-day group at enrolment; patients, personnel administering the intervention and outcome assessors were not blinded), and very serious imprecision (only one study with few patients and/or few events).

It is important to note that this publication only presents initial results from the first 400 patients in a trial that includes 6000 patients (NCT04292899). This analysis will be updated when results from the full cohort are available (the primary completion date of the trial is listed as June 2020).

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [14].

Based on the available evidence, it remains uncertain whether a 5-day treatment schedule of remdesivir is more effective and safer than a 10-day treatment schedule.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect Size</th>
<th>CI 95%</th>
<th>Risk of Bias</th>
<th>Imprecision</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality 14 days after commencing treatment</strong></td>
<td>Odds Ratio 0.73</td>
<td>(CI 95% 0.37 - 1.44)</td>
<td>9 Critical</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases all-cause mortality (total no of events = 37)</td>
</tr>
<tr>
<td><strong>Acute respiratory failure or ARDS Up to 30 days following completion of treatment</strong></td>
<td>Odds Ratio 0.44</td>
<td>(CI 95% 0.21 - 0.93)</td>
<td>9 Critical</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment decreases acute respiratory failure or ARDS slightly (total no of events = 34)</td>
</tr>
<tr>
<td><strong>Septic shock Up to 30 days following completion of treatment</strong></td>
<td>Odds Ratio 0.39</td>
<td>(CI 95% 0.07 - 2.02)</td>
<td>9 Critical</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (total no of events = 7)</td>
</tr>
<tr>
<td><strong>Clinical recovery 14 days after commencing treatment</strong></td>
<td>Odds Ratio 1.56</td>
<td>(CI 95% 1.04 - 2.33)</td>
<td>6 Important</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment affects clinical recovery (total no of events = 235)</td>
</tr>
<tr>
<td><strong>Discharged from hospital 14 days after commencing treatment</strong></td>
<td>Odds Ratio 1.37</td>
<td>(CI 95% 0.92 - 2.04)</td>
<td>6 Important</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases number of patients discharged from hospital (total no of events = 223)</td>
</tr>
<tr>
<td><strong>Serious adverse events Up to 30 days following completion of treatment</strong></td>
<td>Odds Ratio 0.5</td>
<td>(CI 95% 0.32 - 0.79)</td>
<td>9 Critical</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment decreases serious adverse events (total no of events = 110)</td>
</tr>
<tr>
<td>Event Type</td>
<td>Odds Ratio</td>
<td>CI 95%</td>
<td>Difference</td>
<td>Risk of Bias</td>
<td>Imprecision</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>------------</td>
<td>----------------------</td>
<td>------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Serious adverse events (Day 5)</strong></td>
<td>0.62</td>
<td>0.37 - 1.03</td>
<td>73 fewer</td>
<td>Very Low</td>
<td>Very Serious</td>
</tr>
<tr>
<td><strong>Important</strong></td>
<td>228</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events (Up to 30 days following completion of treatment)</strong></td>
<td>0.86</td>
<td>0.55 - 1.33</td>
<td>30 fewer</td>
<td>Very Low</td>
<td>Very Serious</td>
</tr>
<tr>
<td><strong>Important</strong></td>
<td>736</td>
<td>705</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events (Day 5)</strong></td>
<td>0.92</td>
<td>0.62 - 1.38</td>
<td>20 fewer</td>
<td>Very Low</td>
<td>Very Serious</td>
</tr>
<tr>
<td><strong>Important</strong></td>
<td>619</td>
<td>599</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Discontinuation due to adverse events</strong></td>
<td>0.62</td>
<td>0.26 - 1.46</td>
<td>26 fewer</td>
<td>Very Low</td>
<td>Very Serious</td>
</tr>
<tr>
<td><strong>Important</strong></td>
<td>71</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time to recovery Days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Important</strong></td>
<td>11 (Median)</td>
<td>10 (Median)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to low number of patients experiencing event.
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. **Imprecision: Very Serious.** Low number of patients, only data from one study.


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. **Imprecision: Very Serious.** Low number of patients, only data from one study.


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. **Imprecision: Very Serious.** Low number of patients, only data from one study.


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. **Imprecision: Very Serious.** Low number of patients, only data from one study, due to [reason].


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. **Imprecision: Very Serious.** Low number of patients, only data from one study, due to [reason].


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. **Imprecision: Very Serious.** Low number of patients, only data from one study, due to [reason].


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. **Imprecision: Very Serious.** Only data from one study, low number of patients, due to [reason].


18. **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. **Imprecision: Very Serious.** Low number of patients, only data from one study, due to [reason].


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. **Imprecision: Very Serious.** Low number of patients, only data from one study, due to [reason].

21. **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. **Imprecision: Very Serious.** Low number of patients, only data from one study, due to [reason].
### 5.6 - Ruxolitinib

**Strong Recommendation Against**

For people with COVID-19, only administer ruxolitinib in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

---

**Key Info**

<table>
<thead>
<tr>
<th>Benefits and harms</th>
<th>Important harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms. Although most of the information on side effects and harms is derived from long-term use, potential harms include thrombocytopenia and other haematological adverse reactions and increased incidence of bacterial and other infections.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Certainty of the Evidence</th>
<th>Very Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certainty of the evidence is low for mortality and very low for all other outcomes due to serious risk of bias (lack of blinding of outcome assessors) and very serious imprecision (due to the low number of patients and observed events).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preference and values</th>
<th>Substantial variability is expected or uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resources and other considerations</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equity</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Because the benefit to harm ratio is uncertain, it is worth noting that this recommendation will protect more vulnerable populations, such as children.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acceptability</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment is probably acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.</td>
<td></td>
</tr>
</tbody>
</table>
Rationale
There is currently limited evidence about the impact of ruxolitinib on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that these treatments should only be administered in the context of randomised trials with appropriate ethical approval.

Clinical Question/ PICO

| Population: | Patients with COVID-19 |
| Intervention: | Ruxolitinib |
| Comparator: | Placebo |

Summary
Evidence informing this recommendation comes from a single randomised trial that compared ruxolitinib to placebo (vitamin C) in 41 hospitalised adult patients with severe COVID-19 [50].

Certainty of the evidence is low for all-cause mortality and very low for all other outcomes. This judgement is based on serious risk of bias due to lack of blinding of outcome assessors, and very serious imprecision due to the low number of patients and observed events and the reliance on a single study. Mortality was not downgraded for risk of bias as this outcome is unlikely to be biased by lack of blinding.

The Therapeutic Goods Administration highlights several potential side effects associated with the use of ruxolitinib, including thrombocytopaenia and other haematological adverse reactions and increased incidence of bacterial and other infections. Cases of progressive multifocal leukoencephalopathy (PML) and non-melanoma skin cancer have also been reported in patients treated with ruxolitinib [53].

Based on the available evidence, there remains significant uncertainty whether ruxolitinib is more effective and safer than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (Day 28)</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.13 (CI 95% 0.01 - 2.67) Based on data from 41 patients in 1 studies.</td>
<td>143 per 1000</td>
<td>Low Due to very serious imprecision</td>
<td>We are uncertain whether ruxolitinib increases or decreases all-cause mortality (day 28; total no of events = 3)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.19 (CI 95% 0.01 - 4.22) Based on data from 41 patients in 1 studies.</td>
<td>95 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether ruxolitinib increases or decreases septic shock (total no of events = 2)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Effect Size</td>
<td>Confidence Interval</td>
<td>P (95%)</td>
<td>Risk of Bias</td>
<td>Risk of Imprecision</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>---------</td>
<td>--------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Clinical improvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 14 of treatment</td>
<td>Odds Ratio 2</td>
<td>(CI 95% 0.58 - 6.94)</td>
<td>Based on data from 41 patients in 1 studies.</td>
<td>6</td>
<td>Important</td>
</tr>
<tr>
<td></td>
<td>Difference: 171 more per 1000</td>
<td>(CI 95% 125 fewer - 410 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Odds Ratio 1.35</td>
<td>(CI 95% 0.36 - 5.04)</td>
<td>Based on data from 41 patients in 1 studies.</td>
<td>6</td>
<td>Important</td>
</tr>
<tr>
<td>Within 28 days after commencing treatment</td>
<td>Difference: 65 more per 1000</td>
<td>(CI 95% 160 fewer - 383 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Odds Ratio 0.09</td>
<td>(CI 95% 0 - 1.89)</td>
<td>Based on data from 41 patients in 1 studies.</td>
<td>6</td>
<td>Important</td>
</tr>
<tr>
<td>Within 28 days after commencing treatment</td>
<td>Difference: 169 fewer per 1000</td>
<td>(CI 95% 190 fewer - 117 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical deterioration</td>
<td>Odds Ratio 0.09</td>
<td>(CI 95% 0 - 1.89)</td>
<td>Based on data from 41 patients in 1 studies.</td>
<td>6</td>
<td>Important</td>
</tr>
<tr>
<td>At day 14 of treatment</td>
<td>Difference: 169 fewer per 1000</td>
<td>(CI 95% 190 fewer - 117 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Odds Ratio 0.22</td>
<td>(CI 95% 0.04 - 1.24)</td>
<td>Based on data from 41 patients in 1 studies.</td>
<td>6</td>
<td>Important</td>
</tr>
<tr>
<td>Within 28 days after commencing treatment</td>
<td>Difference: 234 fewer per 1000</td>
<td>(CI 95% 313 fewer - 49 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to improvement</td>
<td>Lower better 15 (Median) (Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median days to improvement</td>
<td>15 (Median)</td>
<td>CI 95%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to discharge</td>
<td>Lower better 17 (Median) (Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median days to discharge</td>
<td>16 (Median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce
5.7 - Chloroquine

**Strong Recommendation Against**

For people with COVID-19, only administer chloroquine in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).
### Key Info

#### Benefits and harms

In addition to uncertainty around the benefits for patients with COVID-19, there are well-known harms, with potentially severe adverse events. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold.

#### Certainty of the Evidence

Certainty of the evidence for each outcome is very low. This is based on serious risk of bias due to non-blinding of participants and personnel and incomplete outcome data, and very serious imprecision due to the low number of patients and/or events for some outcomes and the reliance on a single study.

#### Preference and values

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

#### Resources and other considerations

We have no systematically collected evidence regarding cost-benefit.

#### Equity

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

#### Acceptability

Treatment is likely to be acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.

#### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. In addition, although chloroquine is registered on the Australian Register of Therapeutic Goods (ARTG), it is not marketed in Australia and is therefore not readily available.

### Rationale

There is currently limited evidence about the impact of chloroquine on patient-relevant outcomes for COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that disease-modifying treatments should only be administered in the context of randomised trials with appropriate ethical approval.
Clinical Question/ PICO

**Population:** Patients with COVID-19  
**Intervention:** Chloroquine  
**Comparator:** Standard care

Summary

Evidence informing this recommendation comes from a single randomised trial that compared chloroquine plus standard care to standard care alone in 30 hospitalised patients with moderate COVID-19 [37]. Inclusion was limited to patients aged 18 years and older. It is unclear if pregnant women were eligible for inclusion.

The study results are only available as a preprint paper (posted to medRxiv on 22 June 2020) and have therefore not been peer-reviewed. We follow up with the corresponding author every two months to request an update on the study's publication status.

Reported outcomes include all-cause mortality, disease progression (from moderate to critical/severe), adverse events, median time to clinical recovery and median time from randomisation to termination of oxygen therapy. The study did not report results for respiratory failure or ARDS, or the requirement for mechanical ventilation/ECMO.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias (lack of blinding of patients, personnel and outcome assessors, and incomplete reporting of data) and very serious imprecision (low number of patients and/or low number of observed events, and the reliance on a single study).

Although listed on the Australian Register of Therapeutic Goods (ARTG), chloroquine is not marketed in Australia and is not available for general use. Based on the available evidence, there remains significant uncertainty whether chloroquine is more effective and safer than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
</table>
| **All-cause mortality**      | Based on data from 30 patients in 1 studies.  
Within 28 days after commencing treatment  
9 Critical  
(Randomized controlled) | Standard care  
Chloroquine | Very Low  
Due to serious risk of bias and very serious imprecision  
(0.68 - 10.46) | There were no deaths |
| **Progression to severe or critical disease** | Based on data from 30 patients in 1 studies.  
Within 28 days after commencing treatment  
6 Important  
(Randomized controlled) | Standard care  
Chloroquine | Very Low  
Due to serious risk of bias and very serious imprecision  
(0.68 - 10.46) | No patients progressed to severe or critical disease |
| **Adverse events**           | Relative risk 2.67  
Within 28 days  
(CI 95% 0.68 - 10.46) | 167  
446 | Very Low  
Due to serious | We are uncertain whether chloroquine |
### 1. Systematic review [31] with included studies: Chen L 2020

#### Baseline/comparator
Control arm of reference used for intervention.

#### 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.
- Incomplete data and/or large loss to follow up. **Imprecision: Very Serious**. Low number of patients. Only data from one study.

#### Imprecision: Very Serious
- Low number of patients. Only data from one study.

### 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. **Imprecision: Very Serious**. Low number of patients. Only data from one study.

### 3. Systematic review [31] with included studies: Chen L 2020

#### Baseline/comparator
Control arm of reference used for intervention.

#### 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. **Imprecision: Very Serious**. Low number of patients. Only data from one study.

#### Imprecision: Very Serious
- Low number of patients. Only data from one study.

### 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, Incomplete data and/or large loss to follow up. **Imprecision: Very Serious**. Low number of patients. Only data from one study.

### 5. Systematic review [31] with included studies: Chen L 2020

#### Baseline/comparator
Control arm of reference used for intervention.

#### 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. **Imprecision: Very Serious**. Low number of patients. Only data from one study.

#### Imprecision: Very Serious
- Low number of patients. Only data from one study.

### 6. Risk of bias: Serious
- Incomplete data and/or large loss to follow up, 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. **Imprecision: Very Serious**. Low number of patients. Only data from one study.

### 7. Risk of bias: Serious
- Incomplete data and/or large loss to follow up, 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. **Imprecision: Very Serious**. Low number of patients. Only data from one study.

### Table: Differences in Risk of Serious Adverse Events After Commencing Treatment

<table>
<thead>
<tr>
<th>After Commencing Treatment</th>
<th>Baseline/Comparator:</th>
<th>Per 1000</th>
<th>Per 1000</th>
<th>Risk of Bias and Very Serious Imprecision</th>
<th>Increases or Decreases Adverse Events (Total No of Events = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Important</td>
<td>Control Arm of Reference Used for Intervention</td>
<td>Based on Data from 30 Patients in 1 Studies</td>
<td>Difference: 279 More per 1000 (CI 95% 53 Fewer - 1,580 More)</td>
<td>Very Low Due to Serious Risk of Bias and Very Serious Imprecision</td>
<td>There Were No Serious Adverse Events</td>
</tr>
</tbody>
</table>

### Table: Time to Clinical Recovery

<table>
<thead>
<tr>
<th>Time to Clinical Recovery</th>
<th>Median Time to Clinical Recovery (Days)</th>
<th>Measured by: Median time to clinical recovery; chloroquine: 5.5 days (IQR 3.25-7.5); control: 7.5 days (IQR 5.0-16.25)</th>
<th>Lower Better (Randomized Controlled)</th>
<th>Very Low Due to Serious Risk of Bias and Very Serious Imprecision</th>
<th>We Are Uncertain Whether Chloroquine Increases or Decreases Time to Clinical Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Important</td>
<td></td>
<td>7.5 (Median)</td>
<td>5.5 (Median)</td>
<td>CI 95%</td>
<td></td>
</tr>
</tbody>
</table>

### Table: Time to Termination of Oxygen Therapy

<table>
<thead>
<tr>
<th>Time to Termination of Oxygen Therapy</th>
<th>Median Time from Randomisation to Termination of Oxygen Therapy (Days)</th>
<th>Measured by: Median time to termination of oxygen therapy; chloroquine: 8.5 days (IQR 0-9.25); control: 8 days (IQR 3.25-14)</th>
<th>Lower Better (Randomized Controlled)</th>
<th>Very Low Due to Serious Risk of Bias and Very Serious Imprecision</th>
<th>We Are Uncertain Whether Chloroquine Increases or Decreases Time to Termination of Oxygen Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Important</td>
<td></td>
<td>8 (Median)</td>
<td>8.5 (Median)</td>
<td>CI 95%</td>
<td></td>
</tr>
</tbody>
</table>

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. Incomplete data and/or large loss to follow up. **Imprecision: Very Serious**. Low number of patients. Only data from one study.
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. Incomplete data and/or large loss to follow up. **Imprecision: Very Serious**. Low number of patients. Only data from one study.
6. **Risk of bias: Serious**. Incomplete data and/or large loss to follow up. 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. **Imprecision: Very Serious**. Low number of patients. Only data from one study.
7. **Risk of bias: Serious**. Incomplete data and/or large loss to follow up. 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. **Imprecision: Very Serious**. Low number of patients. Only data from one study.
5.8 - Hydroxychloroquine

**Strong Recommendation Against**

For people with COVID-19, only administer hydroxychloroquine in the context of randomised trials with appropriate ethical approval.

The Taskforce notes the release of the press statement from the chief investigators of the RECOVERY trial on 5 June that found no clinical benefit from using hydroxychloroquine in hospitalised patients with COVID-19. On 4 July WHO announced the hydroxychloroquine treatment arm of the Solidarity Trial had been discontinued with immediate effect. We await publication of the results of both trials.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

**Key Info**

**Benefits and harms**

In addition to uncertainty around the benefits for patients with COVID-19, there are well-known harms, with potentially severe adverse events. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold. Long-term harms include retinopathy and chronic cardiac myopathy, among several others.

**Certainty of the Evidence**

Certainty of the evidence for each outcome is very low due to serious risk of bias and the low numbers of trials and patients for some outcomes. There was also inconsistency in the results across trials.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently
Rationale

There is currently limited evidence about the impact of hydroxychloroquine on patient-relevant outcomes for COVID-19. The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects. We therefore recommend that disease-modifying treatments should only be administered in the context of randomised trials with appropriate ethical approval.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Hydroxychloroquine
Comparator: Standard care

Summary

Evidence informing this recommendation comes from four randomised trials that compared hydroxychloroquine sulfate plus standard care to standard care alone [24][25][28][37]. Three studies focused on patients experiencing moderate illness [24][25][37] and one on patients with mild, moderate and severe illness [28].

Each study was limited in the number of relevant outcomes reported. All four reported the number of individuals experiencing one or more adverse events (three studies reported the incidence of severe adverse events [25][28][37] and two studies reported virological clearance at day 7 after treatment initiation [24][28] and mortality [25][37]). None reported the incidence of respiratory failure/ARDS or requirement for mechanical ventilation/ECMO.

Certainty of the evidence for each outcome is very low. This judgement is based on: serious risk of bias due to unclear reporting of sequence generation and allocation concealment [24][25] and lack of blinding of patients and personnel [28][37]; and very serious imprecision due to the low number of patients and/or low number of observed events. The exceptions were adverse events and mortality, in which certainty was low due to serious risk of bias and imprecision.
According to the Therapeutic Goods Administration known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiac myopathy [30]. There are several known and potential interactions with other drugs [30]. Overdose of hydroxychloroquine may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms [30].

Based on the available evidence, there remains significant uncertainty whether hydroxychloroquine/chloroquine is more effective and safer than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>End of treatment</td>
<td>Based on data from 60 patients in 2 studies. (Randomized controlled)</td>
<td>Low Due to serious risk of bias and imprecision</td>
<td>There were no deaths in the studies that reported mortality</td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>End of treatment</td>
<td>3</td>
<td></td>
<td>No studies were found that looked at respiratory failure or ARDS</td>
</tr>
<tr>
<td>Mechanical ventilation or ECMO</td>
<td>End of treatment</td>
<td>4</td>
<td></td>
<td>No studies were found that looked at mechanical ventilation or ECMO</td>
</tr>
<tr>
<td>Negative PCR</td>
<td>Day 7 of treatment</td>
<td>Relative risk 0.93 (CI 95% 0.76 - 1.14) Based on data from 180 patients in 2 studies. (Randomized controlled)</td>
<td>489 per 1000 455 per 1000 Difference: 34 fewer per 1000 (CI 95% 117 fewer - 68 more)</td>
<td>Very Low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>End of treatment</td>
<td>Relative risk 3.01 (CI 95% 1.63 - 5.59) Based on data from 272 patients in 4 studies. (Randomized controlled)</td>
<td>80 per 1000 241 per 1000 Difference: 161 more per 1000 (CI 95% 50 more - 367 more)</td>
<td>Low We are uncertain whether hydroxychloroquine increases or decreases adverse events (total no of events = 46)</td>
</tr>
<tr>
<td>Serious adverse</td>
<td></td>
<td></td>
<td>Very Low We are uncertain whether hydroxychloroquine increases or decreases adverse events (total no of events = 46)</td>
<td>There were too few SAEs in the studies that</td>
</tr>
</tbody>
</table>
For people with COVID-19, only administer convalescent plasma in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms
There is uncertainty around the benefits and harms associated with the use of convalescent plasma for patients with COVID-19.

**Certainty of the Evidence**

Certainty of the evidence is low for mortality and very low all other outcomes due to serious risk of bias (lack of blinding of outcome assessors) and very serious imprecision (due to the low number of patients and observed events).

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Because the benefit to harm ratio is uncertain, it is worth noting that this recommendation will protect more vulnerable populations, such as children.

**Acceptability**

Treatment is probably not acceptable to all patients and clinicians since it is a blood product. However, we have no systematically collected evidence regarding acceptability.

**Feasibility**

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Rationale**

There is currently limited evidence about the impact of convalescent plasma on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that this treatment should only be administered in the context of randomised trials with appropriate ethical approval.

**Clinical Question/ PICO**

- **Population:** Patients with COVID-19
- **Intervention:** Convalescent plasma
- **Comparator:** Standard care
Summary

Evidence informing this recommendation comes from a single randomised trial that compared convalescent plasma to standard care in 103 hospitalised adult patients with severe or critical COVID-19 [48].

Certainty of the evidence is low for all-cause mortality and very low for all other outcomes. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and observed events and the reliance on a single study. Mortality was not downgraded for risk of bias as this outcome is unlikely to be biased by lack of blinding.

Information pertaining to the safety of convalescent plasma for the treatment of COVID-19 is not currently available. The present study did not clearly state the total number of adverse events associated with its use.

Based on the available evidence, there remains significant uncertainty whether convalescent plasma is more effective and safer than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.59 (CI 95% 0.22 - 1.59) Based on data from 101 patients in 1 studies.</td>
<td>Control 240 per 1000</td>
<td>Low Due to very serious imprecision²</td>
<td>We are uncertain whether convalescent plasma increases or decreases all-cause mortality (total no of events = 20)</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>Plasm 157 per 1000</td>
<td>Difference: 83 fewer per 1000 (CI 95% 175 fewer - 94 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 1.42 (CI 95% 0.65 - 3.09) Based on data from 103 patients in 1 studies.</td>
<td>Control 431 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision⁴</td>
<td>We are uncertain whether convalescent plasma improves or worsens clinical improvement (total no of events = 49)</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
<td>Plasm 518 per 1000</td>
<td>Difference: 87 more per 1000 (CI 95% 101 fewer - 270 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 1.85 (CI 95% 0.83 - 4.1) Based on data from 101 patients in 1 studies.</td>
<td>Control 360 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision⁶</td>
<td>We are uncertain whether convalescent plasma increases or decreases hospital discharge (total no of events = 44)</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
<td>Plasm 509 per 1000</td>
<td>Difference: 150 more per 1000 (CI 95% 42 fewer - 338 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral nucleic acid negative (72 hours)</td>
<td>72 hours after commencing treatment</td>
<td>Odds Ratio 11.39 (CI 95% 3.91 - 33.18) Based on data from 87 patients in 1 studies.</td>
<td>Control 375 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision⁸</td>
<td>We are uncertain whether convalescent plasma increases or decreases viral nucleic acid negative (72 hours; total no of events = 56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasm 872 per 1000</td>
<td>Difference: 497 more per 1000 (CI 95% 326 more - 577 more)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.10 - Interferon β-1a

Strong Recommendation Against

For people with COVID-19, only administer interferon β-1a in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms

In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms associated with the use of interferon β-1a including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation.

Certainty of the Evidence

Certainty of the evidence is low for mortality and very low for all other outcomes due to very serious risk of bias (lack of blinding, non-reporting of allocation method and potential for missing outcome data) and very serious imprecision (low number of patients and observed events).
Rationale
There is currently limited evidence about the impact of interferon β-1a on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that this treatment should only be administered in the context of randomised trials with appropriate ethical approval.

<table>
<thead>
<tr>
<th>Preference and values</th>
<th>Substantial variability is expected or uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resources and other considerations</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equity</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Because the benefit to harm ratio is uncertain, it is worth noting that this recommendation will protect more vulnerable populations, such as children.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acceptability</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment is probably acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.</td>
<td></td>
</tr>
</tbody>
</table>

Rationale
There is currently limited evidence about the impact of interferon β-1a on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that this treatment should only be administered in the context of randomised trials with appropriate ethical approval.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Interferon beta-1a</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary
Evidence informing this recommendation comes from a single randomised trial that compared interferon beta-1a with standard care in 81 hospitalised adult patients with severe COVID-19 [49].

The study results are only available as a preprint paper (posted to medRxiv on 30 May 2020) and have therefore not been peer-reviewed. We follow up with the corresponding author every two months to request an update on the study’s publication status.
Certainty of the evidence is low for all-cause mortality and very low for all other outcomes. This judgement is based on serious risk of bias due to lack of blinding and insufficient information regarding allocation concealment and potential missing outcome data, and very serious imprecision due to the low number of patients and observed events and the reliance on a single study. Mortality was not downgraded for risk of bias as this outcome is unlikely to be biased by lack of blinding.

The Therapeutic Goods Administration highlights several potential side effects associated with the use of interferon beta-1a, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation. The use of interferon beta-1a is also associated with immune reactions that can produce flu-like symptoms. 

Based on the available evidence, there remains significant uncertainty whether interferon beta-1a is more effective and safer than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.3 (CI 95% 0.11 - 0.83) Based on data from 81 patients in 1 studies. ¹ (Randomized controlled)</td>
<td>436 per 1000&lt;br&gt;Difference: 248 fewer per 1000 (CI 95% 358 fewer - 45 fewer)</td>
<td>Low Due to very serious imprecision ²</td>
<td>We are uncertain whether interferon beta-1a decreases all-cause mortality (day 28; total no of events = 25)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.72 (CI 95% 0.29 - 1.76) Based on data from 81 patients in 1 studies. ³ (Randomized controlled)</td>
<td>436 per 1000&lt;br&gt;Difference: 78 fewer per 1000 (CI 95% 253 fewer - 140 more)</td>
<td>Very Low Due to very serious risk of bias and very serious imprecision ⁴</td>
<td>We are uncertain whether interferon beta-1a decreases or increases mechanical ventilation (total no of events = 32)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 1.88 (CI 95% 0.64 - 5.47) Based on data from 91 patients in 1 studies. ⁵ (Randomized controlled)</td>
<td>143 per 1000&lt;br&gt;Difference: 96 more per 1000 (CI 95% 47 fewer - 334 more)</td>
<td>Very Low Due to very serious risk of bias and very serious imprecision ⁶</td>
<td>We are uncertain whether interferon beta-1a improves or worsens septic shock (total no of events = 17)</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 1.96 (CI 95% 0.77 - 5.01) Based on data from 81 patients in 1 studies. ⁷ (Randomized controlled)</td>
<td>590 per 1000&lt;br&gt;Difference: 148 more per 1000 (CI 95% 64 fewer - 288 more)</td>
<td>Very Low Due to very serious risk of bias and very serious imprecision ⁸</td>
<td>We are uncertain whether interferon beta-1a increases or decreases time to discharge from hospital</td>
</tr>
</tbody>
</table>
### Duration of hospital stay

<table>
<thead>
<tr>
<th>Mean days to discharge</th>
<th>Difference:</th>
<th>Imprecision:</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.3 (Mean)</td>
<td>MD 2.55 higher</td>
<td>Very Low</td>
</tr>
<tr>
<td>14.8 (Mean)</td>
<td>(CI 95% 0.92 lower - 6.02 higher)</td>
<td>Due to very serious risk of bias and very serious imprecision</td>
</tr>
</tbody>
</table>

**1.** Systematic review [46] with included studies: Davoudi-Monfared 2020. **Baseline/comparator:** Control arm of reference used for intervention.

**2.** **Imprecision:** Very Serious. Low number of patients, Only data from one study.

**3.** Systematic review [46] with included studies: Davoudi-Monfared 2020. **Baseline/comparator:** Control arm of reference used for intervention.

**4.** **Risk of bias:** Very Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

**5.** Systematic review [46] with included studies: Davoudi-Monfared 2020. **Baseline/comparator:** Control arm of reference used for intervention.

**6.** **Risk of bias:** Very Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

**7.** Systematic review [46] with included studies: Davoudi-Monfared 2020. **Baseline/comparator:** Control arm of reference used for intervention.

**8.** **Risk of bias:** Very Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

**9.** Systematic review [46] with included studies: Davoudi-Monfared 2020. **Baseline/comparator:** Control arm of reference used for intervention.

**10.** **Risk of bias:** Very Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

---

**5.11 - Colchicine**

**Strong Recommendation Against**

For adults with COVID-19, only administer colchicine in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).
### Key Info

#### Benefits and harms
In addition to uncertainty around the benefits for patients with COVID-19, there are known side effects and harms associated with colchicine, including diarrhoea. Overdose of colchicine can cause severe diarrhoea and dehydration, bone marrow suppression, metabolic acidosis and shock.

#### Certainty of the Evidence
Certainty of the evidence for each outcome is low or very low due to very serious imprecision (low number of patients and reliance on a single study) and serious risk of bias.

#### Preference and values
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

#### Resources and other considerations
We have no systematically collected evidence regarding cost-benefit.

### Rationale
There is currently limited evidence about the impact of colchicine on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that colchicine should only be administered in the context of randomised trials with appropriate ethical approval.

### Clinical Question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Colchicine  
**Comparator:** Standard care

### Summary
Evidence informing this recommendation comes from a single randomised trial that compared colchicine plus usual care to usual care alone in 105 hospitalised patients with laboratory-confirmed SARS-CoV-2 infection [39]. Eligible patients were adults aged 18 years or older; pregnant and breastfeeding patients were excluded.

Reported outcomes include all-cause mortality, clinical deterioration (reduction of 2 points on the clinical status scale based on the WHO R&D Blueprint Committee definition), requirement of mechanical ventilation, adverse events, serious adverse events and discontinuation due to adverse events. Outcomes were measured within three weeks following randomisation or until hospital discharge.

Certainty of the evidence is low for all-cause mortality, mechanical ventilation, clinical deterioration and discontinuation due to adverse events. This judgement is based on very serious imprecision due to the reliance on a single study and the low number of patients and/or low number of observed events. Certainty of the evidence for adverse events and serious adverse events is very low due to the serious imprecision specified above and serious risk of bias. Patients, personnel involved in administering treatment and outcome assessors were not blinded, which may have affected the reporting and/or severity of these events.

According to the Therapeutic Goods Administration, known acute harms for colchicine include diarrhoea or stomach cramps. Colchicine overdose can cause severe diarrhoea and dehydration, bone marrow suppression, metabolic acidosis and shock [38]. There are several known and potential interactions with other drugs [38]. Colchicine should be avoided in pregnancy and during lactation and in children under 2 years of age. Caution should be taken when prescribing colchicine to elderly patients who may be more susceptible to cumulative toxicity.

### Outcome

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.23 (CI 95% 0.03 - 1.97) Based on data from 105 patients in 1 studies. (Randomized controlled)</td>
<td>80 per 1000</td>
<td>Low Due to very serious imprecision ²</td>
<td>There were too few who experienced all-cause mortality to determine whether colchicine makes a difference (total no of events = 5)</td>
</tr>
<tr>
<td>Within 21 days after commencing treatment</td>
<td></td>
<td>18 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Relative risk 0.15 (CI 95% 0.02 - 1.22) Based on data from 105 patients in 1 studies. (Randomized controlled)</td>
<td>120 per 1000</td>
<td>Low Due to very serious imprecision ⁴</td>
<td>There were too few who experienced mechanical ventilation to determine whether colchicine makes a difference (total no of events = 7)</td>
</tr>
<tr>
<td>Within 21 days after commencing treatment</td>
<td></td>
<td>18 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 2.61 (CI 95% 1.67 - 4.07) Based on data from 105 patients in 1 studies. (Randomized controlled)</td>
<td>300 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious</td>
<td>We are uncertain whether colchicine increases or decreases adverse events (total no of events = 58)</td>
</tr>
<tr>
<td>Within 21 days after commencing treatment</td>
<td></td>
<td>783 per 1000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 21 days after commencing treatment</td>
<td>Relative risk 0.23 (CI 95% 0.03 - 1.97) Based on data from 105 patients in 1 studies. (Randomized controlled)</td>
<td>80 per 1000</td>
<td>Low Due to very serious imprecision ²</td>
<td>There were too few who experienced all-cause mortality to determine whether colchicine makes a difference (total no of events = 5)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Within 21 days after commencing treatment</td>
<td>Relative risk 0.15 (CI 95% 0.02 - 1.22) Based on data from 105 patients in 1 studies. (Randomized controlled)</td>
<td>120 per 1000</td>
<td>Low Due to very serious imprecision ⁴</td>
<td>There were too few who experienced mechanical ventilation to determine whether colchicine makes a difference (total no of events = 7)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Within 21 days after commencing treatment</td>
<td>Relative risk 2.61 (CI 95% 1.67 - 4.07) Based on data from 105 patients in 1 studies. (Randomized controlled)</td>
<td>300 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious</td>
<td>We are uncertain whether colchicine increases or decreases adverse events (total no of events = 58)</td>
</tr>
</tbody>
</table>

2. **Risk of bias:** No 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. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


4. **Risk of bias:** No 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. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


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. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


8. **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. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

---

**Serious adverse events**

Within 21 days after commencing treatment

- **6 Important**

**Baseline/comparator:** Control arm of reference used for intervention.

**Risk of bias:** No 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. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

**Imprecision**

There were no serious adverse events

---

**Clinical deterioration**

Within 21 days after commencing treatment

- **6 Important**

**Baseline/comparator:** Control arm of reference used for intervention.

**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. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

**Imprecision**

There were too few who experienced clinical deterioration to determine whether colchicine makes a difference (total no of events = 8)

---

**Discontinuation due to adverse events**

Within 21 days after commencing treatment

- **6 Important**

**Baseline/comparator:** Control arm of reference used for intervention.

**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. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

**Imprecision**

There were too few who experienced discontinuation due to adverse events to determine whether colchicine makes a difference (total no of events = 2)

10. Risk of bias: No 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. Imprecision: Very Serious. Only data from one study, Low number of patients.


12. Risk of bias: No 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. Imprecision: Very Serious. Low number of patients, Only data from one study.

5.12 - Other disease-modifying treatments

Consensus Recommendation

For people with COVID-19, only administer disease-modifying treatments in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates regarding the use of these treatments, the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms

Currently, there is no direct evidence available to inform the potential benefits or harms of other disease-modifying treatments in patients with COVID-19.

Certainty of the Evidence

We have no COVID-19 specific randomised trials for many of the potential disease-modifying treatments.

Preference and values

We have no systematically collected information regarding patients' preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to take risks.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

Important issues, or potential issues not investigated

Important issues, or potential issues not investigated
There is currently limited evidence about the impact of other disease-modifying treatments on patient-relevant outcomes in COVID-19. The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

In line with the ANZICS, ASID, AHPPC and IDSA recommendations[5][7][22][23], we therefore recommend that disease-modifying treatments should only be administered in the context of randomised trials with appropriate ethical approval.

### Acceptability

Depending on the kind of treatment, the treatments are probably acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.

### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

There is currently limited evidence about the impact of other disease-modifying treatments on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

In line with the ANZICS, ASID, AHPPC and IDSA recommendations[5][7][22][23], we therefore recommend that disease-modifying treatments should only be administered in the context of randomised trials with appropriate ethical approval.

### Adaptation

The recommendation for use of antivirals and other disease-modifying treatments is adapted from published recommendations by ANZICS [5], Surviving Sepsis Campaign [56], JAMA [25], Institute of Tropical Medicine (Belgium) [26], Department of Infectious Diseases at Austin Health (Australia), BMJ Best Practice [6], Alfred Health (Australia) [4], Australasian Society of Infectious Diseases [7], National Institute for the Infectious Diseases (Italy) [3] and Zhejiang University School of Medicine (China) [2].
### 6 - Chemoprophylaxis

#### 6.1 - Hydroxychloroquine for post-exposure prophylaxis

**Strong Recommendation Against**

For people exposed to individuals with COVID-19, only administer hydroxychloroquine for post-exposure prophylaxis in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on chemoprophylaxis. As evidence accumulates the Taskforce will continue to review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

**Key Info**

**Benefits and harms**
In addition to uncertainty around the benefits for patients with COVID-19, there are well-known harms, with potentially severe adverse events. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold. Long-term harms include retinopathy and chronic cardiac myopathy, among several others.

There are several known and potential interactions with other drugs. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses. In pregnancy, it is only recommended when benefits outweigh harms.

**Certainty of the Evidence**
Certainty of the evidence is low or very low due to very serious imprecision based on the reliance on a single trial and low number of events for some outcomes.

**Preference and values**
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to take risks.

**Resources and other considerations**
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

**Equity**
We have no systematically collected direct evidence regarding impact on equity. There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Because the benefit to harm ratio is uncertain, it is worth noting that this recommendation will protect more vulnerable populations, such as children.

**Acceptability**
Treatment is likely to be acceptable to both patients and clinicians. However, we have not systematically collected evidence
Rationale

There is currently limited evidence about the impact of prophylactic hydroxychloroquine on the prevention of infection in people exposed to COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that chemoprophylaxis should only be administered in the context of randomised trials with appropriate ethical approval.

Clinical Question/ PICO

| Population: | People exposed to COVID-19 |
| Intervention: | Hydroxychloroquine post-exposure prophylaxis |
| Comparator: | Placebo |

Summary

Evidence informing this recommendation comes from a single randomised trial that compared post-exposure prophylaxis using hydroxychloroquine to placebo [55]. All people included in the trial were asymptomatic at the time of the first dose of treatment (100 randomised patients were excluded from the analysis due to developing symptoms after randomisation but prior to commencement of treatment).

Certainty of the evidence is very low to low for all outcomes due to serious or very serious imprecision based on low number of patients and/or low number of observed events, risk of bias and the reliance on a single study.

According to the Therapeutic Goods Administration known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiac myopathy [30]. There are several known and potential interactions with other drugs [30]. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses. In pregnancy, it is only recommended when benefits outweigh harms [30].

Based on the available evidence, there remains significant uncertainty whether post-exposure prophylactic hydroxychloroquine is more effective at preventing COVID-19 infection than placebo.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory confirmed diagnosis</td>
<td></td>
<td>Odds Ratio 1.21 (CI 95% 0.49 - 2.94) Based on data from 821 patients in 1 studies.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 per 1000</td>
<td>26 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very Low Due to serious risk of bias and very serious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>We are uncertain whether hydroxychloroquine post-exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event Description</td>
<td>Summary</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>Low Risk of Bias and Imprecision</td>
<td>Discontinuation due to adverse events during treatment</td>
</tr>
<tr>
<td>-------------------</td>
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<td>------------</td>
<td>-------</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Systematic review [54] with included studies: Boulware 2020. <strong>Baseline/comparator:</strong> Control arm of reference used for 14 days after commencing treatment</td>
<td>Difference: 4 more per 1000 (CI 95% -11 fewer - 40 more)</td>
<td>0.84</td>
<td>(CI 0.55 - 1.27)</td>
<td>(Randomized controlled)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Symptoms compatible with COVID-19</strong>: 3 14 days after commencing treatment</td>
<td>Odds Ratio 0.84</td>
<td>0.54 - 1.27</td>
<td>Based on data from 821 patients in 1 studies.</td>
<td>(Randomized controlled)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Confirmed or probable infection</strong>: 6 14 days after commencing treatment</td>
<td>Odds Ratio 0.81</td>
<td>0.54 - 1.21</td>
<td>Based on data from 821 patients in 1 studies.</td>
<td>(Randomized controlled)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong>: Within 14 days after commencing treatment</td>
<td>Based on data from 821 patients in 1 studies.</td>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td><strong>Adverse events</strong>: Within 14 days after commencing treatment</td>
<td>Odds Ratio 3.32</td>
<td>2.33 - 4.72</td>
<td>Based on data from 700 patients in 1 studies.</td>
<td>(Randomized controlled)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Discontinuation due to adverse events</strong>: During treatment</td>
<td>Odds Ratio 2.14</td>
<td>0.91 - 5.01</td>
<td>Based on data from 821 patients in 1 studies.</td>
<td>(Randomized controlled)</td>
<td>Very Low</td>
</tr>
</tbody>
</table>
2. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up. **Imprecision:** Very Serious. Only data from one study and few events.

3. The presence of one or more compatible symptoms, which could include diarrhea. Based on the "Council of State and Territorial Epidemiologists interim standardized surveillance case definition and national notification for 2019 novel coronavirus disease"


5. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up. **Imprecision:** Serious. Only data from one study.

6. Confirmed cases: positivity for SARS-CoV-2 on PCR assay; probable cases: the presence of cough, shortness of breath, or difficulty breathing, or the presence of two or more symptoms of fever, chills, rigors, myalgia, headache, sore throat, and new olfactory and taste disorders.


8. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up. **Imprecision:** Serious. Only data from one study.


10. **Imprecision:** Very Serious. Low number of patients, Only data from one study, no events.


12. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up. **Imprecision:** Serious. Only data from one study.


14. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up. **Imprecision:** Very Serious. Only data from one study and few events.
7 - Respiratory support

Current evidence suggests that about 19% of patients with COVID-19 experience hypoxic respiratory failure, 14% of whom will develop severe disease requiring oxygen therapy and 5% requiring mechanical ventilation within an ICU setting [56]. The majority of early guidelines generally base recommendations on indirect evidence from studies involving SARS, MERS and influenza, although it is presently unclear if patients with COVID-19 would benefit from alternative strategies to optimise the effective administration of respiratory support.

Consensus Recommendation

Guiding principles of care
For patients with COVID-19 for whom respiratory support (HFNO/NIV) is being considered, decisions should balance likelihood of patient benefit against the risk of infection for healthcare workers. For patients with COVID-19 receiving respiratory support (HFNO/NIV) or requiring intubation, use single rooms or negative pressure rooms wherever possible and ensure contact, droplet and airborne precautions are in place.

The relative risk of infection to healthcare workers associated with specific oxygen therapies remains uncertain and may vary from site to site.

7.1 - High-flow nasal oxygen therapy

Recommendation Strength Not Set

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where oxygen is delivered, often in conjunction with compressed air and humidification. It delivers high flow oxygen via large diameter nasal cannula that is humidified and heated. Flow rates can be given up to 60 L/min in adults and 25 L/min in children with an oxygen/air blender supplying oxygen at 21-100%.

High-flow humidified oxygen should be considered when unable to maintain SaO2 ≥ 92% despite conventional oxygen delivery at > 6 L/min or an FiO2 0.4

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: High-flow nasal oxygen therapy
Comparator: Conventional oxygen therapy

Summary
Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 [63].

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### Synthesis method

**Meta-analysis**

**Results**

Included 12 RCTs (n = 2217 patients). Decreased risk of requiring intubation and escalation of oxygen therapy (defined as crossover to HFNC in the control group or initiation of non-invasive or invasive ventilation in either group) in favour of HFNC over conventional oxygen therapy. There was no significant difference in mortality, intensive care unit length of stay, hospital length of stay, patient-reported dyspnea and patient-reported comfort. Treatment-reported complications were not pooled due to variability in reporting but were generally minimal across studies and comparable between interventions.

### Review 2: Risk of dispersal

<table>
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<tr>
<th>Study design</th>
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<tr>
<td>Population</td>
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<td>Comparison</td>
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**Synthesis method**

None, individual study results only

**Results**

Five studies were included, of which three were simulation studies and none were randomised trials. No studies included patients with COVID-19. In summary, the findings were very uncertain and no conclusions could be drawn. One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).

For both reviews, certainty of the evidence is deemed to be low to very low due to indirectness (not based on COVID-19 patients), risk of bias and lack of precision in some outcomes.

### Outcome

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<td>Mortality</td>
<td>Relative risk 0.94 (CI 95% 0.67 - 1.31) Based on data from 1,407 patients in 4 studies. ¹ (Randomized controlled) Follow up 7 to 90 days</td>
<td>Conventional therapy: 272 per 1000 HFNO: 256 per 1000</td>
<td>Low Due to serious imprecision and indirectness ²</td>
<td>HFNO may have little or no difference on mortality</td>
</tr>
</tbody>
</table>

1. Based on available studies, no significant difference in hospital length of stay was observed. Differences in patient-reported dyspnea and comfort across interventions were not significant. Treatment-reported complications were not pooled due to variability in reporting but were generally minimal across studies and comparable between interventions.

2. For both reviews, certainty of the evidence is deemed to be low to very low due to indirectness (not based on COVID-19 patients), risk of bias and lack of precision in some outcomes.
Invasive ventilation

Relative risk 0.85 (CI 95% 0.74 - 0.99)
Based on data from 1,687 patients in 8 studies. 3
Follow up 2 to 28 days

Difference: 43 fewer per 1000 (CI 95% 74 fewer - 3 fewer)

Very Low
Due to serious risk of bias, imprecision and indirectness 4
We are uncertain whether HFNO increases or decreases invasive ventilation

Escalation of therapy (HFNC, NIV or intubation)

Relative risk 0.71 (CI 95% 0.51 - 0.98)
Based on data from 1,703 patients in 8 studies. 5
Follow up 2 to 28 days

Difference: 93 fewer per 1000 (CI 95% 157 fewer - 6 fewer)

Very Low
Due to serious risk of bias, imprecision and indirectness 6
We are uncertain whether HFNO increases or decreases escalation of therapy (HFNC, NIV or intubation)

ICU length of stay (Days)

Based on data from: 972 patients in 2 studies.

Difference: MD 1.38 fewer (CI 95% 0.9 fewer - 3.66 fewer)

Very Low
Due to serious imprecision, inconsistency and indirectness 7
We are uncertain whether HFNO increases or decreases ICU length of stay

Hospital length of stay (Days)

Based on data from: 1,247 patients in 4 studies.

Difference: MD 0.67 more (CI 95% 1.41 fewer - 0.08 more)

Low
Due to serious imprecision and indirectness 8
HFNO may have little or no difference on hospital length of stay

Patient-reported dyspnea

Variable score

Based on data from: 894 patients in 7 studies.

Difference: SMD 0.66 lower (CI 95% 1.68 lower - 0.35 higher)

Very Low
Due to serious risk of bias, imprecision and indirectness 9
We are uncertain whether HFNO improves or worsens patient reported dyspnea

Patient-reported comfort

Variable score

Based on data from: 1,233 patients in 7 studies.

Difference: SMD 0.12 lower (CI 95% 0.61 lower - 0.37 higher)

Very Low
Due to serious risk of bias, imprecision, inconsistency and indirectness 10
We are uncertain whether HFNO improves or worsens patient reported comfort

Dispersal of droplets and aerosols

One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not

Very Low
Due to serious risk of bias and indirectness 11
We are uncertain whether HFNO increases or decreases dispersal of droplets and aerosols
In negative pressure rooms, use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety. Use the lowest flow necessary to maintain oxygen saturation $\geq 92\%$.

**Clinical Question/ PICO**

- **Population:** Patients with COVID-19
- **Intervention:** High-flow nasal oxygen therapy
- **Comparator:** Conventional oxygen therapy

**Summary**

Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 [63].

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</tr>
<tr>
<td>Synthesis method</td>
<td>Meta-analysis</td>
</tr>
</tbody>
</table>
Results

Included 12 RCTs (n = 2217 patients). Decreased risk of requiring intubation and escalation of oxygen therapy (defined as crossover to HFNC in the control group or initiation of non-invasive or invasive ventilation in either group) in favour of HFNC over conventional oxygen therapy. There was no significant difference in mortality, intensive care unit length of stay, hospital length of stay, patient-reported dyspnea and patient-reported comfort. Treatment-reported complications were not pooled due to variability in reporting but were generally minimal across studies and comparable between interventions.

Review 2: Risk of dispersal

Study design | Simulation studies and one prospective crossover study
---|---
Population | Healthy adult volunteers (two simulation studies), model human patient simulators (two simulation studies), and critically ill patients who received supplemental oxygen therapy (one crossover study). No studies available in patients with COVID-19, which was considered a limitation in applicability (indirect evidence).
Intervention | High-flow nasal oxygen (HFNO)
Comparison | None (three simulation studies); CPAP (one simulation study); conventional therapy with face mask (one crossover study)
Synthesis method | None, individual study results only

Results

Five studies were included, of which three were simulation studies and none were randomised trials. No studies included patients with COVID-19. In summary, the findings were very uncertain and no conclusions could be drawn. One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).

For both reviews, certainty of the evidence is deemed to be low to very low due to indirectness (not based on COVID-19 patients), risk of bias and lack of precision in some outcomes.

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<tr>
<td>Mortality</td>
<td>Critical</td>
<td>Relative risk 0.94 (CI 95% 0.67 - 1.31) Based on data from 1,407 patients in 4 studies. (^1) (Randomized controlled) Follow up 7 to 90 days</td>
<td></td>
<td></td>
<td>Low Due to serious imprecision and indirectness (^2) HFNO may have little or no difference on mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>272 per 1000</td>
<td>256 per 1000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 16 fewer per 1000 (CI 95% 90 fewer - 84 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>95% 0.74 - 0.99</td>
<td>Relative risk 0.85 (CI 95%</td>
<td>286</td>
<td>243</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>272</td>
<td>256</td>
<td>Very Low Due to serious</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Randomized controlled
\(^2\) Serious limitations in evidence due to study design and study limitations.
### Escalation of therapy (HFNC, NIV or intubation)

Based on data from 1,687 patients in 8 studies. Follow up 2 to 28 days.

**Risk of bias, imprecision and indirectness**

Relative risk 0.71 (CI 95% 0.51 - 0.98)

**Very Low**

- Increases or decreases invasive ventilation

**Follow up**: 2 to 28 days

**Difference**: 43 fewer per 1000 (CI 95% 74 fewer - 3 fewer)

- **320** per 1000
- **227** per 1000

**Follow up**: 2 to 28 days

**Difference**: 93 fewer per 1000 (CI 95% 157 fewer - 6 fewer)

- **We are uncertain whether HFNO increases or decreases escalation of therapy (HFNC, NIV or intubation)**

### ICU length of stay (Days)

Based on data from 1,703 patients in 8 studies.

**Risk of bias, imprecision and indirectness**

**Very Low**

- Due to serious risk of bias, imprecision and indirectness

**Follow up**: 2 to 28 days

**Difference**: 320 fewer per 1000 (CI 95% 95% 74 fewer - 3 fewer)

- **MD 1.38 fewer** (CI 95% 0.9 fewer - 3.66 fewer)

**Follow up**: 2 to 28 days

**Difference**: 227 fewer per 1000 (CI 95% 157 fewer - 6 fewer)

- **MD 0.67 more** (CI 95% 1.41 fewer - 0.08 more)

**Due to serious imprecision and indirectness**

- **Very Low**
- **Low**

**HFNO may have little or no difference on ICU length of stay**

### Hospital length of stay (Days)

Based on data from: 1,247 patients in 4 studies.

**Risk of bias, imprecision and indirectness**

**Low**

- Due to serious imprecision and indirectness

**Follow up**: 2 to 28 days

**Difference**: 1.38 fewer per 1000 (CI 95% 0.9 fewer - 3.66 fewer)

- **MD 0.67 more** (CI 95% 1.41 fewer - 0.08 more)

**Due to serious imprecision and indirectness**

- **Very Low**
- **Low**

**HFNO may have little or no difference on hospital length of stay**

### Patient-reported dyspnea

Variable score

Based on data from: 894 patients in 7 studies.

**Risk of bias, imprecision and indirectness**

**Very Low**

- Due to serious risk of bias, imprecision and indirectness

**Follow up**: 2 to 28 days

**Difference**: 0.66 lower (CI 95% 1.68 lower - 0.35 higher)

- **SMD 0.66 lower** (CI 95% 1.68 lower - 0.35 higher)

**Due to serious risk of bias, imprecision and indirectness**

- **Very Low**
- **Low**

**We are uncertain whether HFNO improves or worsens patient-reported dyspnea**

### Patient-reported comfort

Variable score

Based on data from: 1,233 patients in 7 studies.

**Risk of bias, imprecision, inconsistency and indirectness**

**Very Low**

- Due to serious risk of bias, imprecision, inconsistency and indirectness

**Follow up**: 2 to 28 days

**Difference**: 0.12 lower (CI 95% 0.61 lower - 0.37 higher)

- **SMD 0.12 lower** (CI 95% 0.61 lower - 0.37 higher)

**Due to serious risk of bias, imprecision, inconsistency and indirectness**

- **Very Low**
- **Low**

**We are uncertain whether HFNO improves or worsens patient-reported comfort**

### Dispersal of droplets and aerosols

Based on data from 972 patients in 2 studies.

**Risk of bias, imprecision and indirectness**

**Very Low**

- Due to serious risk of bias, imprecision and indirectness

**Follow up**: 2 to 28 days

**Difference**: 1.38 fewer per 1000 (CI 95% 0.9 fewer - 3.66 fewer)

- **MD 0.67 more** (CI 95% 1.41 fewer - 0.08 more)

**Due to serious imprecision and indirectness**

- **Very Low**
- **Low**

**We are uncertain whether HFNO increases or decreases ICU length of stay**

- **HFNO may have little or no difference on hospital length of stay**

### Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce

One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in more dispersion.
Weak Recommendation

In single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, consider using high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.

Clinical Question/ PICO

Population: Patients with COVID-19

Intervention: High-flow nasal oxygen therapy

Comparator: Conventional oxygen therapy

Summary

Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 [63].

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in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).
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**Review 2: Risk of dispersal**

**Study design**
Simulation studies and one prospective crossover study

**Population**
Healthy adult volunteers (two simulation studies), model human patient simulators (two simulation studies), and critically ill patients who received supplemental oxygen therapy (one crossover study). No studies available in patients with COVID-19, which was considered a limitation in applicability (indirect evidence).

**Intervention**
High-flow nasal oxygen (HFNO)

**Comparison**
None (three simulation studies); CPAP (one simulation study); conventional therapy with face mask (one crossover study)

**Synthesis method**
None, individual study results only

Five studies were included, of which three were simulation studies and none were randomised trials. No studies included patients with COVID-19. In summary, the findings were very uncertain and no conclusions could be drawn. One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).

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<td>Relative risk 0.85 (CI 95% 0.74 - 0.99)</td>
<td>Conventional therapy: 286 HFNO: 243</td>
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<td>We are uncertain whether HFNO</td>
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<td>per 1000</td>
<td>per 1000</td>
<td>risk of bias, imprecision and indirectness 4 increases or decreases invasive ventilation...</td>
<td></td>
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<td>Difference: 93 fewer per 1000 ( CI 95% 157 fewer - 6 fewer )</td>
<td><strong>Very Low</strong> Due to serious imprecision, inconsistency and indirectness 7</td>
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<td></td>
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<td>Difference: <strong>SMD 0.12 lower</strong> ( CI 95% 0.61 lower - 0.37 higher )</td>
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</tr>
<tr>
<td>Patient-reported dyspnea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>We are uncertain whether HFNO increases or decreases dispersal of droplets and aerosols</td>
</tr>
<tr>
<td>Variable score</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Strong Recommendation Against

In shared wards or emergency department cubicles do not use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: High-flow nasal oxygen therapy
Comparator: Conventional oxygen therapy

Summary

Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 [63].

Review 1: Effectiveness

<table>
<thead>
<tr>
<th>Study design</th>
<th>Randomised trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>High-flow nasal cannula (HFNC)</td>
</tr>
<tr>
<td>Comparison</td>
<td>Conventional oxygen therapy</td>
</tr>
<tr>
<td>Synthesis method</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Results</td>
<td>Included 12 RCTs (n = 2217 patients). Decreased risk of requiring intubation and escalation of oxygen therapy (defined as crossover to HFNC in the control group or initiation of non-invasive or invasive ventilation in either group) in favour of HFNC over...</td>
</tr>
</tbody>
</table>
conventional oxygen therapy. There was no significant difference in mortality, intensive care unit length of stay, hospital length of stay, patient-reported dyspnea and patient-reported comfort. Treatment-reported complications were not pooled due to variability in reporting but were generally minimal across studies and comparable between interventions.

Review 2: Risk of dispersal

<table>
<thead>
<tr>
<th>Study design</th>
<th>Simulation studies and one prospective crossover study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Healthy adult volunteers (two simulation studies), model human patient simulators (two simulation studies), and critically ill patients who received supplemental oxygen therapy (one crossover study). No studies available in patients with COVID-19, which was considered a limitation in applicability (indirect evidence).</td>
</tr>
<tr>
<td>Intervention</td>
<td>High-flow nasal oxygen (HFNO)</td>
</tr>
<tr>
<td>Comparison</td>
<td>None (three simulation studies); CPAP (one simulation study); conventional therapy with face mask (one crossover study)</td>
</tr>
<tr>
<td>Synthesis method</td>
<td>None, individual study results only</td>
</tr>
</tbody>
</table>

Results

Five studies were included, of which three were simulation studies and none were randomised trials. No studies included patients with COVID-19. In summary, the findings were very uncertain and no conclusions could be drawn. One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).

For both reviews, certainty of the evidence is deemed to be low to very low due to indirectness (not based on COVID-19 patients), risk of bias and lack of precision in some outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conventional therapy</td>
<td>HFNO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>272 per 1000</td>
<td>256 per 1000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative risk 0.94</td>
<td>(CI 95% 0.67 - 1.31)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>Critical</td>
<td>Based on data from 1,407 patients in 4 studies. 1 (Randomized controlled)</td>
<td>Difference: 16 few er per 1000 ( CI 95% 90 fewer - 84 more )</td>
<td>Low Due to serious imprecision and indirectness 2</td>
<td>HFNO may have little or no difference on mortality</td>
</tr>
<tr>
<td></td>
<td>November</td>
<td>Follow up 7 to 90 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>286 per 1000</td>
<td>243 per 1000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Critical</td>
<td>Relative risk 0.85 (CI 95% 0.74 - 0.99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>November</td>
<td>Based on data from 1,687 patients in 8 studies. 3</td>
<td>Difference: 43 fewer per 1000 ( CI 95% 74 fewer - 3 fewer )</td>
<td>Very Low Due to serious risk of bias, imprecision and indirectness 4</td>
<td>We are uncertain whether HFNO increases or decreases invasive ventilation</td>
</tr>
</tbody>
</table>
### Escalation of therapy (HFNC, NIV or intubation)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Relative risk 0.71 (CI 95% 0.51 - 0.98)</th>
<th>Based on data from 1,703 patients in 8 studies.</th>
<th>Very Low</th>
<th>Difference: 93 fewer per 1000 (CI 95% 157 fewer - 6 fewer)</th>
<th>We are uncertain whether HFNO increases or decreases escalation of therapy (HFNC, NIV or intubation)</th>
</tr>
</thead>
</table>

Follow up 2 to 28 days

### ICU length of stay (Days)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Based on data from: 972 patients in 2 studies.</th>
<th>Very Low</th>
<th>Difference: MD 1.38 fewer (CI 95% 0.9 fewer - 3.66 fewer)</th>
<th>We are uncertain whether HFNO increases or decreases ICU length of stay</th>
</tr>
</thead>
</table>

### Hospital length of stay (Days)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Based on data from: 1,247 patients in 4 studies.</th>
<th>Low</th>
<th>Difference: MD 0.67 more (CI 95% 1.41 fewer - 0.08 more)</th>
<th>HFNO may have little or no difference on hospital length of stay</th>
</tr>
</thead>
</table>

### Patient-reported dyspnea

<table>
<thead>
<tr>
<th>Effect</th>
<th>Based on data from: 894 patients in 7 studies.</th>
<th>Very Low</th>
<th>Difference: SMD 0.66 lower (CI 95% 1.68 lower - 0.35 higher)</th>
<th>We are uncertain whether HFNO improves or worsens patient reported dyspnea</th>
</tr>
</thead>
</table>

### Patient-reported comfort

<table>
<thead>
<tr>
<th>Effect</th>
<th>Based on data from: 1,233 patients in 7 studies.</th>
<th>Very Low</th>
<th>Difference: SMD 0.12 lower (CI 95% 0.61 lower - 0.37 higher)</th>
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### Dispersal of droplets and aerosols

<table>
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<tr>
<th>Effect</th>
<th>One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).</th>
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<th>Due to serious risk of bias and indirectness</th>
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1. Systematic review with included studies: [61]. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.**
3. Systematic review with included studies: [61]. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** **Indirectness: Serious.** **Imprecision: Serious.**
5. Systematic review with included studies: [61]. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias:** Serious. **Indirectness:** Serious. **Imprecision:** Serious.
7. **Indirectness:** Serious. **Imprecision:** Serious.
8. **Indirectness:** Serious. **Imprecision:** Serious.
9. **Risk of bias:** Serious. **Indirectness:** Serious. **Imprecision:** Serious.
10. **Risk of bias:** Serious. **Inconsistency:** Serious. **Indirectness:** Serious. **Imprecision:** Serious.
11. **Risk of bias:** Serious. Substantial risk of bias in all five studies. **Inconsistency:** No serious. **Indirectness:** Serious. No studies included patients with COVID-19. **Imprecision:** No serious. **Publication bias:** No serious.

**Strong Recommendation Against**

During *inter-hospital patient transfer/retrieval* do not use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19.

**Clinical Question/ PICO**

- **Population:** Patients with COVID-19
- **Intervention:** High-flow nasal oxygen therapy
- **Comparator:** Conventional oxygen therapy

**Summary**

Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 [63].

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<td>Conventional therapy: 272 per 1000</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>HFNO: 256 per 1000</td>
<td></td>
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<td>Invasive ventilation</td>
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<td>Very Low Due to serious risk of bias, imprecision and indirectness</td>
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<td></td>
</tr>
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<td>Escalation of therapy (HFNC, NIV or intubation)</td>
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<td>Conventional therapy: 320 per 1000</td>
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7.2 - Non-invasive ventilation

Non-invasive ventilation (NIV), also known as non-invasive positive pressure ventilation (NIPPV) or bilevel positive pressure support (BiPAP), is a form of respiratory support. Bilevel positive pressure is delivered throughout the respiratory cycle by a firm-fitting nasal-face mask. The patient breathes spontaneously and triggers the device to cycle.

A higher level of pressure is provided during the inspiratory phase to enhance ventilation, while a lower level of continuous positive pressure is delivered during the expiratory phase (also known as positive end-expiratory pressure or PEEP). Supplemental oxygen can also be delivered through the device.

Consensus Recommendation

In negative pressure rooms, consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Rationale

Non-invasive ventilation (NIV) may be associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolisation with poor mask fit.

Adaptation

The recommendation is adapted from published recommendations by ANZICS [5]. Wording has been adapted for clarity and applicability to the Australian context.

Consensus Recommendation

In single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Rationale

Non-invasive ventilation (NIV) may be associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolisation with poor mask fit.
Adaptation
The recommendation is adapted from published recommendations by ANZICS [5]. Wording has been adapted for clarity and applicability to the Australian context.

**Consensus Recommendation**

In **shared wards or emergency department cubicles**, do not use NIV therapy for patients with hypoxaemia associated with COVID-19.

**Rationale**
Routine use of non-invasive ventilation (NIV) is not recommended as it may be associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolisation with poor mask fit.

Adaptation
The recommendation is adapted from published recommendations by ANZICS [5]. Wording has been adapted for clarity and applicability to the Australian context.

**Consensus Recommendation**


**Rationale**
Routine use of non-invasive ventilation (NIV) is not recommended as it may be associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolisation with poor mask fit.

Adaptation
The recommendation is adapted from published recommendations by ANZICS [5]. Wording has been adapted for clarity and applicability to the Australian context.

**Consensus Recommendation**

In patients with COVID-19 for whom NIV is appropriate for an alternate clinical presentation (e.g. concomitant COPD with type 2 respiratory failure and hypercapnoea, APO), ensure airborne and other infection control precautions are optimised.

**Rationale**
Routine use of non-invasive ventilation (NIV) is not recommended as it may be associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolisation with poor mask fit.

Adaptation
The recommendation is adapted from published recommendations by ANZICS [5]. Wording has been adapted for clarity and applicability to the Australian context.
7.3 - Respiratory management of the deteriorating patient

Consensus Recommendation

In patients with COVID-19 who are deteriorating, consider early endotracheal intubation and invasive mechanical ventilation. *Patients can deteriorate rapidly 5 to 10 days after onset of symptoms.*

Adaptation

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [56]. Wording has been adapted for clarity and applicability to the Australian context.

7.4 - Videolaryngoscopy

Weak Recommendation

In adults with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy if available and the operator is trained in its use.

Key Info

Benefits and harms

Time to intubation varied depending on the experience of the operator and the setting. Another important consideration is the potential risk of contamination to the operator due to the infectious nature of COVID-19. In a simulation study using a manikin, the distance between the operator and patient’s mouth increased when using video compared to direct laryngoscopy, thus potentially benefitting operators in the case of COVID-19.

Certainty of the Evidence

For the two critical outcomes—distance between patient and operator, and time to successful intubation—certainty of the evidence is very low due to serious risk of bias, inconsistency, indirectness and imprecision.

Preference and values

We have no systematically collected information regarding patients’ preferences and values. Although there is uncertainty regarding the time to successful intubation, we are reasonably confident that patients would find videolaryngoscopy an acceptable intervention compared to direct laryngoscopy.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. The main costs associated with videolaryngoscopy are attributed to the initial equipment outlay, maintenance and operator training. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

Equity

There is a risk of creating inequity as people who live in rural and remote areas may have limited access to videolaryngoscopy and experienced operators. Due to costs and maintenance, there will be variation in the type of clinical settings likely to have...
access to the appropriate equipment; larger, specialised centres in urban areas are more likely to provide access than those in smaller more remote centres.

The panel noted that rural and remote hospitals do not routinely have access to videolaryngoscopy. The outcome of time to successful intubation is dependent on operator expertise and would likely take longer in non-specialist centres. However, the panel felt that most people intubating would be trained in videolaryngoscopy, although experience would vary. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

Acceptability

Videolaryngoscopy is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility

Feasibility is affected by the initial equipment costs, maintenance and operator training. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

Rationale

Videolaryngoscopy allows for increased distance between operator and patient.

Clinical Question/ PICO

| Population: | Patients requiring emergency intubation |
| Intervention: | Videolaryngoscopy |
| Comparator: | Direct laryngoscopy |

Summary

Evidence informing this recommendation comes from a systematic review of video versus direct laryngoscopy for the emergency intubation of adults in the inpatient setting [70]. A simulation study is also included that evaluated the distance between a dummy's mouth and physician's face during intubation [75].

Effectiveness and adverse events

| Study design | Randomised trials |
| Population: | Critically ill patients requiring emergency intubation in emergency departments or intensive care units. No studies available in patients with COVID-19. |
| Intervention: | Videolaryngoscopy |
| Comparison: | Direct laryngoscopy |
| Synthesis method | Meta-analysis |

Results

We included six of the eight randomised trials (1023 patients) in the Rombey review [68][69][71][72][73][74]. (Two were excluded because patients were intubated before hospital admission.) We included an additional randomised trial of 163 patients that was published after the Rombey review [67]. This study did not change the overall results for the outcomes, but did improve the precision of the estimate for inadvertent oesophageal intubation.

There was no difference between video and direct laryngoscopy with respect to successful intubation at first attempt or time to successful intubation. In the four randomised trials that reported inadvertent oesophageal intubation, the use of videolaryngoscopy was associated with fewer of these adverse events, however the number was small (27 events).
### Operator distance (Hall 2020)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Crossover study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>25 doctors of mixed experience performing tracheal intubation on a high-fidelity manikin.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Videolaryngoscopy</td>
</tr>
<tr>
<td>Comparison</td>
<td>Direct laryngoscopy</td>
</tr>
<tr>
<td>Results</td>
<td>Videolaryngoscopy may extend the mouth-to-mouth distance from laryngoscopist to patient compared to direct laryngoscopy.</td>
</tr>
</tbody>
</table>

Certainty of the evidence is low to very low due to indirectness (not based on COVID-19 patients or exclusively patients with ARDS), risk of bias, lack of precision in some outcomes and small number of adverse events.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
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<tr>
<td>First-pass intubation success</td>
<td>Relative risk 1.05 (CI 95% 0.94 - 1.17) Based on data from 1,186 patients in 7 studies. (^1) (Randomized controlled)</td>
<td>716 per 1000 752 per 1000</td>
<td>Very Low Due to serious risk of bias, inconsistency and indirectness (^2)</td>
<td>We are uncertain whether videolaryngoscopy increases or decreases first-pass intubation success.</td>
</tr>
<tr>
<td>Oesophageal intubation</td>
<td>Relative risk 0.4 (CI 95% 0.17 - 0.93) Based on data from 795 patients in 4 studies. (^3) (Randomized controlled)</td>
<td>50 per 1000 20 per 1000</td>
<td>Low Due to serious risk of bias and indirectness (^4)</td>
<td>Videolaryngoscopy may decrease oesophageal intubation.</td>
</tr>
<tr>
<td>Operator distance in cm (^5) 8 Critical</td>
<td>Measured by: distance analysed from videorecording High better Based on data from: 25 patients in 1 studies. (^6) (Randomized controlled)</td>
<td>16.4 centimetres (Mean) 35.6 centimetres (Mean)</td>
<td>Very Low Due to serious risk of bias, indirectness and imprecision (^7)</td>
<td>Videolaryngoscopy may increase the operator distance.</td>
</tr>
<tr>
<td>Time to successful intubation 7 Critical</td>
<td>Based on data from 988 patients in 6 studies.</td>
<td>The heterogeneity for this outcome was too high to combine in a meta-analysis. Two studies reported shorter time to successful intubation with direct laryngoscopy, two with videolaryngoscopy, and two reported the same or very similar durations.</td>
<td>Very Low Due to serious risk of bias, indirectness and imprecision, and very serious inconsistency (^8)</td>
<td>We are uncertain whether videolaryngoscopy increases or decreases time to successful intubation.</td>
</tr>
</tbody>
</table>

---

7.5 - Neuromuscular blockers

Neuromuscular blocking agents (NMBAs) are a pharmaceutical intervention that may facilitate protective lung ventilation in patients who are mechanically ventilated with moderate to severe acute respiratory distress syndrome (ARDS). NMBAs may reduce patient-ventilator dysynchrony and facilitate improved oxygenation by various mechanisms, including reducing the inspiratory muscle effort and the work of breathing, and reducing ventilator-induced lung injury.
**Weak Recommendation Against**

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs).

*However, if protective lung ventilation cannot be achieved, consider using NMBAs for up to 48 hours. If indicated, consider cisatracurium as first-line agent, if cisatracurium is not available alternatives include atracurium or vecuronium by infusion.*

---

**Key Info**

**Benefits and harms**

Small net benefit, or little difference between alternatives

There is no substantial net benefit to using neuromuscular blockers. Prolonged use of NMBAs could have negative effects on intubated patients, such as muscle weakness and difficulty weaning from mechanical ventilation.

**Certainty of the Evidence**

Very Low

Outcomes identified as most critical were 90-day mortality and muscle weakness at 28 days. No studies were identified that included patients with COVID-19. Certainty of the evidence for all outcomes is very low, mostly due to serious inconsistency, indirectness and imprecision. There were substantial methodological inconsistencies between the trials.

**Preference and values**

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients’ preferences and values. Since there is uncertainty regarding the critical outcome of muscle weakness, some patients might consider NMBAs unacceptable. The inability to move or communicate while being treated with neuromuscular blockers is likely to be an additional consideration for patients.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. There are potential resource considerations due to supply issues for some neuromuscular blockers (e.g. cisatracurium).

**Equity**

Important issues, or potential issues not investigated

There is a risk of creating inequity as some populations may have limited access to neuromuscular blockers, particularly if there is a shortage.

**Acceptability**

Important issues, or potential issues not investigated

Neuromuscular blockers may be less acceptable because of possible harms—patients and clinicians may consider the benefits are not worth the risk. In addition to the risk of muscle weakness, patients and their families may deem it unacceptable to be paralysed and non-responsive.

**Feasibility**

Important issues, or potential issues not investigated

Feasibility may be affected by potential supply issues for some neuromuscular blockers (e.g. cisatracurium).

**Rationale**

Routine use of continuous infusions of neuromuscular blockers could have negative effects on intubated patients, such as muscle weakness and difficulty weaning from mechanical ventilation.
Clinical Question/ PICO

**Population:** Mechanically ventilated adults with COVID-19 and persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation or persistently high plateau pressures

**Intervention:** Continuous infusion of NMBA

**Comparator:** No continuous infusion of NMBA

Summary

Evidence informing this recommendation comes from five randomised trials involving 1461 adults with acute respiratory distress syndrome. Currently, there is no evidence in patients with COVID-19. The five trials compared continuous infusions of neuromuscular blocking agents with cisatracurium for up to 48 hours to no continuous infusions of NMBA [77][78][79][80][81].

For all critical outcomes, it is uncertain whether infusion of neuromuscular blockers makes a difference. The ROSE trial, which had a different sedation strategy to the other trials and implemented a higher PEEP strategy, is the largest (1006 participants) and most recent trial, and may be the most reflective of current practice [78]. There were no differences for the mortality outcomes, but the trial found a small increase in muscle weakness at 28 days in the neuromuscular blocker group.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>28-day mortality</strong></td>
<td>Relative risk 0.78 (CI 95% 0.58 - 1.06) Based on data from 1,461 patients in 5 studies. [1] (Randomized controlled)</td>
<td>372 per 1000 290 per 1000 Difference: 82 fewer per 1000 (CI 95% 156 fewer - 22 more)</td>
<td>Very Low Due to serious inconsistency, indirectness and imprecision [2]</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen 28-day mortality (total no of events in trials = 513).</td>
</tr>
<tr>
<td><strong>90-day mortality</strong></td>
<td>Relative risk 0.81 (CI 95% 0.62 - 1.06) Based on data from 1,461 patients in 5 studies. [3] (Randomized controlled)</td>
<td>441 per 1000 357 per 1000 Difference: 84 fewer per 1000 (CI 95% 168 fewer - 26 more)</td>
<td>Very Low Due to serious inconsistency, indirectness and imprecision [4]</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen 90-day mortality (total no of events in trials = 612).</td>
</tr>
<tr>
<td><strong>ICU mortality</strong></td>
<td>Relative risk 0.72 (CI 95% 0.57 - 0.91) Based on data from 455 patients in 4 studies. [5] (Randomized controlled)</td>
<td>438 per 1000 315 per 1000 Difference: 123 fewer per 1000 (CI 95% 188 fewer - 39 fewer)</td>
<td>Very Low Due to serious imprecision and very serious indirectness [6]</td>
<td>We are uncertain whether neuromuscular blockers increase or decrease ICU mortality (total no of events in trials = 171).</td>
</tr>
<tr>
<td><strong>ICU weakness at day 28</strong></td>
<td>Relative risk 1.23 (CI 95% 0.81 - 1.88) Based on data from 356 patients in 4 studies. [7] (Randomized controlled)</td>
<td>230 per 1000 283 per 1000 Difference: 53 more per 1000 (CI 95% 44 fewer - 202 more)</td>
<td>Very Low Due to serious risk of bias and imprecision, and very serious indirectness [8]</td>
<td>We are uncertain whether neuromuscular blockers increase or decrease ICU weakness at day 28 (total no of events in trials = 91).</td>
</tr>
</tbody>
</table>
Baseline/comparator: Control arm of reference used for intervention.

2. Inconsistency: Serious. The magnitude of statistical heterogeneity was high, with I²:50 %. Clinical heterogeneity - ROSE trial has a different sedation strategy than the other trials. 
Indirectness: Serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. Only one study (largest study) used a high PEEP strategy. 
Imprecision: Serious. Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. 
Publication bias: No serious.

Baseline/comparator: Control arm of reference used for intervention.

4. Inconsistency: Serious. The magnitude of statistical heterogeneity was high, with I²:2.56 %. Clinical heterogeneity - ROSE trial has a different sedation strategy than the other trials. 
Indirectness: Serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. 
Imprecision: Serious. Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. 
Publication bias: No serious.

Baseline/comparator: Control arm of reference used for intervention.

6. Inconsistency: No serious. Indirectness: Very Serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. The largest trial, with the most applicable strategy reflecting current clinical practice, did not report on on this outcome. 
Imprecision: Serious. The largest trial did not report on this outcome. 
Publication bias: No serious.

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.
Inconsistency: No serious. Indirectness: Very Serious. Differences between the population of interest and those studied: no studies in COVID-19 patients. The largest trial, with the most applicable strategy reflecting current clinical practice, only included a very small subset of patients for this outcome. Imprecision: Serious. Low number of patients. Publication bias: No serious.
10. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inconsistency: Serious. Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. Indirectness: Serious. Differences between the population of interest and those studied: no studies in COVID-19 patients. Imprecision: No serious. Publication bias: No serious.
14. Risk of bias: Serious. Inconsistency: No serious. Indirectness: Serious. Differences between the population of interest and those studied. Imprecision: Serious. Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. Publication bias: No serious.

7.6 - Positive end-expiratory pressure

**Consensus Recommendation**

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, consider using a higher PEEP strategy (PEEP > 10 cm H2O) over a lower PEEP strategy.

**Rationale**

While there is no current evidence for using a higher PEEP strategy in patients with COVID-19 and moderate to severe ARDS, a higher PEEP strategy is recommended for ventilated patients with moderate to severe ARDS of other aetiologies.

**Adaptation**

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [56].
7.7 - Prone positioning

**Recommendation Strength Not Set**

Positioning the patient in a face-down (prone) position may help to open up (recruit) collapsed alveoli and improve oxygen levels in the blood.

**Consensus Recommendation**

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning. Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff, and that minimises the risk of adverse events, e.g. accidental extubation.

**Adaptation**

The recommendation is adapted from published recommendations by ANZICS [5]. Wording has been adapted for clarity and applicability to the Australian context.

**Consensus Recommendation**

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning. When positioning a patient in prone, ensure it is used with caution and close monitoring of the patient. Patients who are deteriorating should be considered for early endotracheal intubation and invasive mechanical ventilation.

**Rationale**

Prone positioning is used in people with severe hypoxaemic respiratory failure in the context of ARDS. In ventilated people with ARDS, prone positioning improves oxygenation and clinical outcomes. Prone positioning is thought to work by improving tidal ventilation, especially to dependent parts of the lung, enhancing ventilation and perfusion matching as well as favourably distributing the pleural pressures throughout the lung thus minimising further damage.

7.8 - Recruitment manoeuvres

**Recommendation Strength Not Set**

Patients receiving respiratory support are at an increased risk of lung injury. Recruitment manoeuvres are used to open up ('recruit') collapsed alveoli and are a common element of an 'open lung approach' to protect the lungs during mechanical ventilation. The manoeuvres use a sustained increase in airway pressure to re-open collapsed alveoli.

Types of manoeuvres include: prolonged high continuous positive airway pressure; progressive incremental increases in positive end-expiratory pressure at a constant driving pressure (incremental PEEP, stepwise or staircase); and high driving pressures.
Consensus Recommendation

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider using recruitment manoeuvres.

If recruitment manoeuvres are used, do not use staircase or stepwise (incremental PEEP) recruitment manoeuvres.

Adaptation
The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [56]. Wording has been adapted for clarity and applicability to the Australian context.

7.9 - Extracorporeal membrane oxygenation

Recommendation Strength Not Set

Extracorporeal membrane oxygenation (ECMO) is a form of life support that removes blood from the body via large cannulae, oxygenates and removes carbon dioxide from the blood external to the patient, and then returns the blood to the body.

Venovenous (VV) ECMO provides oxygenation support for the lungs only, while venoarterial (VA) ECMO supports the heart and lungs.

Consensus Recommendation

In mechanically ventilated adults with COVID-19 and refractory hypoxaemia (despite optimising ventilation, use of rescue therapies and proning), consider using venovenous extracorporeal membrane oxygenation (VV ECMO) if available, or referring the patient to an ECMO centre.

Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in carefully selected patients with COVID-19 and severe ARDS.

Adaptation
The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [56]. Wording has been adapted for clarity and applicability to the Australian context.
8 - Steroids for people with asthma or COPD and COVID-19

8.1 - Steroids for people with asthma or COPD and COVID-19

Consensus Recommendation

Use inhaled or oral steroids for the management of people with co-existing asthma or COPD and COVID-19 as you would normally for viral exacerbation of asthma or COPD. Do not use a nebuliser.

Key Info

Benefits and harms

Stopping long-term inhaled or oral corticosteroids suddenly can lead to exacerbation of symptoms of asthma and COPD or risk of relative adrenal insufficiency. There is currently no evidence specific to patients with COVID-19 and asthma/COPD.

Certainty of the Evidence

There is no available evidence about outcomes for inhaled or oral corticosteroids for patients with COVID-19 and asthma/COPD.

Preference and values

We have no systematically collected information regarding patients’ preferences and values. The panel believes that, while there is uncertainty about the benefit to harm ratio regarding the use of corticosteroids for COVID-19, there are likely harms associated with an exacerbation of COPD or asthma, as well as harms associated with a sudden stopping of corticosteroids, and thus patients may prefer to take steroids as prescribed.

Resources and other considerations

We have no systematically collected information regarding cost-benefit. Continued use of inhaled or oral corticosteroids as per usual care is unlikely to have an impact on availability of these drugs. At present, the Therapeutic Goods Administration limits dispensing of medicines for asthma/COPD to a maximum of one month’s supply.

Equity

There are no identified equity issues.

Acceptability

For corticosteroids, the treatment is most likely to be acceptable to both patients and clinicians.

Feasibility

As the recommendation reflects usual care there are likely no important feasibility issues.

Rationale

Oral steroids and continuation of inhaled steroids reduce harms in patients experiencing exacerbations of COPD and asthma and are considered usual care. There is currently no evidence to indicate that it is necessary to deviate from usual care.
## Adaptation

The recommendation is adapted from published recommendations from three clinical guidelines, Australian Asthma Handbook, NICE [NG168] and NICE [NG 166]. Wording has been adapted for clarity and applicability to the Australian context.

## Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>People with asthma or COPD and COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

## Summary

For patients with COPD, NICE NG168 recommends that patients who are having an exacerbation for COPD start a course of oral corticosteroids and/or antibiotics if oral corticosteroids and/or antibiotics are clinically indicated. Oral corticosteroids are not recommended for symptoms of COVID-19 alone (e.g. fever, dry cough or myalgia) [83].

NICE NG168 also recommends continuing oral or inhaled steroids, and to avoid stopping or delaying withdrawal of inhaled steroids [83].

Similarly, for patients with severe asthma, NICE NG166 recommends that patients who develop symptoms and signs of an asthma exacerbation should follow their personalised asthma action plan and start a course of oral corticosteroids if clinically indicated [84]. This recommendation is in concordance with the Australian Asthma Handbook, which recommends that clinicians “administer or prescribe systemic (oral) corticosteroids to manage severe flare-ups or acute asthma as indicated, following recommendations based on age-group” but to be cautious using corticosteroids when acute viral infection is suspected or confirmed (e.g. avoid use for mild flare-ups) [82].

For patients with severe asthma, NICE NG166 recommends that patients continue using oral or inhaled steroids and to avoid stopping oral or inhaled steroids [84]. For patients with asthma who are receiving inhaled steroids, the Australian Asthma Handbook also advises patients to continue taking inhaled corticosteroids. It reminds clinicians to warn patients that stopping their preventer increases the risk of severe asthma flare-ups, including those triggered by viral respiratory infections [82].

The recommendations take into consideration potential harms with starting oral corticosteroids (particularly at high doses for a prolonged period) and harms associated with withholding corticosteroids suddenly.

According to the Therapeutic Goods Administration, starting oral corticosteroids (prednisolone or dexamethasone) can lead to disturbed endocrine function, ophthalmological conditions and adrenal suppression [85]/[86].

Abrupt withdrawal of corticosteroids can lead to acute adrenal insufficiency or exacerbation of symptoms of asthma or COPD.

## Outcome

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>See summary</td>
</tr>
</tbody>
</table>

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9 - Anticoagulants

9.1 - Venous thromboembolism (VTE) prophylaxis

**Consensus Recommendation**

Use prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) in adults with moderate COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding. Where severe acute kidney disease is present, unfractionated heparin or renally adjusted doses of LMWH may be used (e.g. enoxaparin 20 mg once daily or dalteparin 2500 IU once daily).

**Key Info**

**Benefits and harms**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Substantial net benefits of the recommended alternative</th>
</tr>
</thead>
</table>

There is uncertainty around benefits and harms for patients with COVID-19, but the benefits as well as harms associated with the use of LMW heparin and other anticoagulants are well-known in other patient groups.

**Certainty of the Evidence**

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Substantial variability is expected or uncertain</th>
</tr>
</thead>
</table>

There is no available evidence regarding outcomes for the use of LMW heparin or other anticoagulants in patients with COVID-19.

**Preference and values**

<table>
<thead>
<tr>
<th>Preference</th>
<th>Substantial variability is expected or uncertain</th>
</tr>
</thead>
</table>

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients may prefer to wait while other patients may be more willing to take risks.

**Resources and other considerations**

<table>
<thead>
<tr>
<th>Resource</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
</table>

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

**Equity**

<table>
<thead>
<tr>
<th>Equity</th>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
</table>

There are no identified equity issues.

**Acceptability**

<table>
<thead>
<tr>
<th>Acceptability</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
</table>

Treatment is probably acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.

**Feasibility**

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
</table>

There are no identified feasibility issues.

**Rationale**

The panel believes that the benefits of pharmacologic prophylaxis among medically ill patients outweigh potential harm, such as bleeding caused by this prophylaxis. The panel believes that this will also apply to patients with COVID-19 and therefore...
recommend pharmacologic prophylaxis.

Adaptation

The recommendation for use of DVT prophylaxis is adapted from published recommendations by the International Society on Thrombosis and Haemostasis [87], University of Miami [88] and British Haematological Society [89]. Wording has been adapted for clarity and applicability to the Australian context.

Clinical Question/ PICO

- **Population:** People with moderate COVID-19
- **Intervention:** DVT prophylaxis
- **Comparator:** Standard care

Summary

At present there are no randomised trials that have investigated the benefits of using anticoagulants in patients with moderate COVID-19. There is variability in existing COVID-19 specific recommendations regarding the use of anticoagulants in COVID-19 patients, such that the use of anticoagulants should be considered in all patients [87][88], all immobilised or severely ill patients [89] or used based on best existing data and best current local practices [90].

Heparin is contraindicated in individuals with ulcerative conditions showing a tendency to haemorrhage (e.g. gastrointestinal ulcer, ulcerative colitis), cerebral haemorrhage, severe thrombocytopaenia or other severe coagulation disorders, and individuals with an uncontrollable active bleeding state. The use of heparin can result in side effects such as haemorrhage, thrombocytopaenia, skin necrosis or irritation at the injection site, and suppression of aldosterone synthesis with hyperkalaemia and/or metabolic acidosis [91][92].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>See summary</td>
<td>Relative risk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**9.2 - Increased-dose venous thromboembolism (VTE) prophylaxis**

**Consensus Recommendation**

Consider using increased prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily) in adults with severe or critical COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding or platelet count < 30 x 10^9/L. Where severe acute kidney disease is present (creatinine clearance < 30 mL/min), unfractionated heparin or renal adjusted doses of LMWH may be used (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily).
**Key Info**

**Benefits and harms**

There is uncertainty around the benefits and harms for patients with COVID-19. However, there are well-known benefits as well as harms associated with the use of LMW heparin and other anticoagulants in other patient groups.

**Certainty of the Evidence**

There is currently no evidence relating to increased prophylactic doses of anticoagulants in patients with COVID-19.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. Since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to take risks.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to treatments by patients currently using them for other indications.

**Equity**

There are no identified equity issues.

**Acceptability**

Treatment is probably acceptable to both patients and clinicians, however, we have no systematically collected evidence regarding acceptability.

**Feasibility**

There are no identified feasibility issues.

**Rationale**

Conventional prophylactic doses of anticoagulants seem less effective in preventing VTE in severe or critically ill COVID-19 patients. It is unclear whether higher doses will improve outcomes but the risk-benefit ratio seems acceptable.

**Clinical Question/ PICO**

- **Population:** Patients with severe or critical COVID-19
- **Intervention:** Increased-dose thromboprophylaxis
- **Comparator:** Conventional treatment

**Summary**

There are no randomised trials comparing increased-dose thromboprophylaxis to conventional treatment in patients with COVID-19 but there are observational studies. Ten studies have reported on the prevalence of venous thromboembolic
(VTE) events in patients with critical or severe COVID-19, ranging from 3.3% to 69% (see Table).

<table>
<thead>
<tr>
<th>Study</th>
<th>Severity of Illness</th>
<th>VTE events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goyal 2020 [71]</td>
<td>Moderate / Critical</td>
<td>13/393 (3.3%)*</td>
</tr>
<tr>
<td>Lodigani 2020 [63]</td>
<td>Severe / Critical</td>
<td>28/362 (7.7%)</td>
</tr>
<tr>
<td>Helms 2020 [67]</td>
<td>Severe / Critical</td>
<td>28/150 (18.7%)</td>
</tr>
<tr>
<td>Middeldorp 2020 [62]</td>
<td>Severe / Critical</td>
<td>39/198 (20%)</td>
</tr>
<tr>
<td>Poissy 2020 [61]</td>
<td>Severe / Critical</td>
<td>22/107 (20.6%)</td>
</tr>
<tr>
<td>Cui 2020 [66]</td>
<td>Severe / Critical</td>
<td>20/81 (25%)</td>
</tr>
<tr>
<td>Klok 2020 [65]</td>
<td>Severe / Critical</td>
<td>75/184 (40.8%)</td>
</tr>
<tr>
<td>Zhang 2020 [68]</td>
<td>Critical</td>
<td>66/143 (46.1%)</td>
</tr>
<tr>
<td>Wichmann 2020 [60]</td>
<td>Critical</td>
<td>7/12 (58%)</td>
</tr>
<tr>
<td>Llitjos 2020 [64]</td>
<td>Severe / Critical</td>
<td>18/26 (69%)</td>
</tr>
</tbody>
</table>

*prevalence was 7.7% and 1.1% in patients receiving and not receiving mechanical ventilation, respectively.

Eight studies were assessed as moderate risk of bias due to low external validity—cohort not representative of the target population and lack of random selection/census. One was at high risk of bias [60] and one was unclear due to limited reporting of methods [71].

One study reported outcomes in patients with moderate to critical COVID-19 who received systemic anticoagulants versus those who did not [70]. Mortality was similar between the groups (22.5% systemic vs 22.8% control). Although more patients receiving systemic anticoagulants required mechanical ventilation (29.8% vs 8.1%), mortality was lower in this group (29.1% vs 62.7%). Major bleeding events were slightly higher in the control group (3.0% vs 1.9%).

A meta-analysis on platelet count in patients with COVID-19 included nine studies (1779 participants) [69]. Platelet count was significantly lower in patients with more severe compared to less severe COVID-19 (mean -31 x 109/L), with the lowest platelet counts linked to mortality (mean -48 x 109/L). The authors concluded that low platelet count is associated with increased risk of severe disease and mortality in patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates control</th>
<th>Prophylaxis</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>See summary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10 - ACEIs/ARBs in patients with COVID-19

10.1 - ACEIs/ARBs in patients with COVID-19

Consensus Recommendation

In patients with COVID-19 who are receiving ACEIs/ARBs, these medications should be continued unless contraindicated (e.g., hypotension).

Key Info

Benefits and harms
Stopping ACEI/ARB medication could lead to acute heart failure or unstable blood pressure. There is currently no randomised trial evidence specific to patients with COVID-19 and the use of ACEIs/ARBs.

Certainty of the Evidence
While there are no randomised trials of ACEIs/ARBs in patients with COVID-19, there are observational studies that seek to determine if there is an association between ACEIs/ARBs and diagnosis of COVID-19 or mortality for patients with a diagnosis of COVID-19.

Preference and values
We have no systematically collected information regarding patients' preferences and values. The panel believes that, while there is uncertainty about the benefit to harm ratio regarding the use of ACEIs/ARBs in patients with COVID-19, there are likely harms associated with stopping ACEIs/ARBs. The panel believes that most patients would prefer to continue their current medication although some may want to discuss benefits and risks of discontinuing treatment.

Resources and other considerations
We have no systematically collected information regarding cost-benefit. Continued use of ACEIs/ARBs as per usual care is unlikely to have an impact on availability of these drugs.

Equity
There are no identified equity issues.

Acceptability
Continued concomitant ACEI/ARB treatment is likely to be acceptable to both patients and clinicians.

Feasibility
As the recommendation reflects usual care there are likely no important feasibility issues.

Rationale
ACEIs/ARBs for people with hypertension, where indicated, are considered usual care. There is currently no evidence to indicate that it is necessary to deviate from usual care.

Adaptation
This recommendation is adapted from published recommendations from numerous Australian and international guidelines and...
position statements [105][106][107][108][109][110][111][112][113][114][115][116][117][118]. Wording has been adapted for clarity and applicability to the Australian context.
## 11 - Pregnancy and perinatal care

### 11.1 - Mode of birth

**Weak Recommendation**

For pregnant women with COVID-19, mode of birth should remain as per usual care.

There is currently no evidence to indicate that caesarean section for women with COVID-19 reduces the risk of vertical transmission to the newborn. Mode of birth should continue as per usual care. Respiratory deterioration due to COVID-19 may prompt urgent delivery on an individual basis.

**Key Info**

- **Benefits and harms**
  
  Evidence informing this recommendation comes from a systematic review of 49 studies comprising 655 women and 666 newborns, of whom 28 newborns (4.2%) had a COVID-19 infection. No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively by mode of birth (vaginal birth or caesarean section).

- **Certainty of the Evidence**
  
  Certainty of the evidence is very low due to reliance on case reports and case series. Evidence informing this recommendation comes from a systematic review estimating the risk of the newborn becoming infected with COVID-19 by mode of birth (vaginal or caesarean) in pregnant women with confirmed or suspected COVID-19 infection.

- **Preference and values**
  
  There is no systematically collected information regarding the preferences and values of pregnant women with COVID-19 at this point. Mode of birth should be individualised, based on clinical indications and taking into consideration individual preferences and values.

- **Resources and other considerations**
  
  We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19 (regardless of mode of birth) requires greater resources than for women without COVID-19. The routine use of caesarean section for all pregnant women with COVID-19 would have additional resource implications.

- **Equity**
  
  For pregnant women with COVID-19, access to on-site paediatric support is needed at the time of birth. This may be more challenging for those women living in rural or remote areas.

- **Acceptability**
  
  Acceptability of different modes of birth by pregnant women is expected to vary and individual preferences should be taken into consideration. Clear communication from health professionals regarding the benefits and harms of different modes of birth is essential to aid discussion around individual preferences and acceptability.

- **Feasibility**
  
  No important issues with the recommended alternative.
Rationale
There is currently no evidence to indicate that caesarean section for pregnant women with COVID-19 reduces the risk of vertical transmission. Usual care practices regarding clinical indications for caesarean section should be used.

No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively by mode of birth (vaginal birth or caesarean section). Therefore, the benefits and harms of mode of birth should be considered as per usual care, taking into consideration relevant clinical indications and a woman's individual preferences. However, clinical deterioration due to worsening COVID-19 may prompt urgent delivery of the baby.

Clinical Question/ PICO

| Population: | Pregnant women with COVID-19 |
| Intervention: | Caesarean section |
| Comparator: | Vaginal birth |

Summary
Evidence informing this recommendation comes from a systematic review that estimated the risk of the newborn becoming infected with COVID-19 by mode of birth (vaginal or caesarean) [119]. The review included 49 case reports or case series comprising 666 newborns. Cases were only included where the mother either had confirmed COVID-19 (based on a positive swab) or a high clinical suspicion of COVID-19 where a swab had not been taken. The incidence of COVID-19 infection in newborns is given in the table below.

<table>
<thead>
<tr>
<th>Mode of birth</th>
<th>Total newborns*</th>
<th>Infected</th>
<th>Not infected</th>
<th>Not tested</th>
<th>Died</th>
<th>% Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>292</td>
<td>8</td>
<td>261</td>
<td>21</td>
<td>7</td>
<td>2.7% (8/292)</td>
</tr>
<tr>
<td>Caesarean</td>
<td>374</td>
<td>20</td>
<td>313</td>
<td>26</td>
<td>1</td>
<td>5.3% (20/374)</td>
</tr>
</tbody>
</table>

*The review authors contacted the first author of the paper where there were missing newborn data (4 hospitals)

No cases of COVID-19 infection met the criteria for confirmed vertical transmission (positive PCR in umbilical cord blood, newborn blood collected within the first 12 hours of birth, or amniotic fluid collected prior to rupture of membranes). It was not possible to apply the classification developed by Shah et al [120] (confirmed, probable, possible, unlikely or not infected) due to lack of virological testing at birth or in first 12 hours of life.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infected newborns</td>
<td>Based on data from 666 patients in 49 studies.</td>
<td>See summary for details. No cases of COVID-19 infection met the criteria for confirmed vertical transmission. Number of infected newborns was reported as 2.7% (8/292) for vaginal birth and 5.3% (20/374) for caesarean section. Based on data from 655 women and 666 newborns.</td>
<td>Very Low Due to very serious risk of bias and serious imprecision and inconsistency ¹</td>
<td>We are uncertain whether caesarean section increases or decreases the number of infected newborns.</td>
</tr>
</tbody>
</table>

1. **Risk of bias: Very Serious.** Evidence is derived from case studies and case reports. **Inconsistency: Serious.** Variations in outcome definitions, disease severity and availability of different testing modalities. **Indirectness: No serious. Imprecision:**

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¹ Determined using the GRADE approach.
Breastfeeding is supported irrespective of the presence of COVID-19. However, women with COVID-19 who are breastfeeding should use infection control and prevention measures (mask and hand hygiene) while infectious.

There is currently no evidence to indicate that breastfeeding increases the risk of vertical transmission to the newborn. There are substantial known benefits for breastfeeding and therefore women should be supported to initiate or continue breastfeeding.

Key Info

**Benefits and harms**

Evidence informing this recommendation comes from a systematic review of 49 studies comprising 655 women and 666 newborns, of whom 28 newborns (4.2%) had a COVID-19 infection. Testing of breastmilk was not reported. Of the 28 newborns infected, seven were breastfed, three formula-fed and one was given expressed breastmilk. The method of infant feeding was not reported for 17 newborns.

**Certainty of the Evidence**

Certainty of the evidence is very low due to reliance on case reports and case series.

**Preference and values**

There is no systematically collected information regarding the preferences and values of pregnant women with COVID-19 at this point. Breastfeeding is an individual decision based on consideration of individual preferences and values.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. However, there is not expected to be any substantial resource considerations for breastfeeding compared to not breastfeeding. Caring for pregnant women and newborns with COVID-19 (irrespective of breastfeeding or not) requires greater resources than for women and newborns without COVID-19.

**Equity**

There are likely no important equity issues.

**Acceptability**

Acceptability of infant feeding practices by pregnant and postpartum women is expected to vary and individual preferences should be taken into consideration. Clear communication from health professionals regarding the benefits and harms of different feeding practices is essential to aid discussion around individual preferences and acceptability.
Feasibility

There are likely no important feasibility issues as the recommendation reflects usual care.

Rationale

There is currently no evidence to indicate that breastfeeding affects the risk of vertical transmission of COVID-19. Usual care practices regarding breastfeeding of newborns should be used.

No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively for different feeding practices, though evidence is currently limited.

Breastfeeding should be considered as per usual care, taking into consideration relevant clinical situation and a woman’s individual preferences.

Clinical Question/ PICO

Population: Pregnant women with COVID-19
Intervention: Exposure of a newborn to breastmilk from mothers with confirmed or suspected COVID-19
Comparator: No exposure of a newborn to breastmilk from mothers with confirmed or suspected COVID-19

Summary

Evidence informing this recommendation comes from a systematic review whose primary purpose was to estimate the risk of the newborn becoming infected with COVID-19 by mode of birth (vaginal or caesarean) [119]. Newborn infection status by method of feeding was also reported (see table). The review included 49 case reports or case series comprising 666 newborns. Cases were only included where the mother either had confirmed COVID-19 (based on a positive swab) or a high clinical suspicion of COVID-19 where a swab had not been taken. No testing of breastmilk was reported.

<table>
<thead>
<tr>
<th>Feeding type</th>
<th>Total newborns</th>
<th>Infected</th>
<th>Not infected</th>
<th>Not tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastmilk</td>
<td>148</td>
<td>7</td>
<td>139</td>
<td>2</td>
</tr>
<tr>
<td>Expressed breastmilk</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Formula</td>
<td>56</td>
<td>3</td>
<td>39</td>
<td>14</td>
</tr>
<tr>
<td>Not reported*</td>
<td>460</td>
<td>17</td>
<td>396</td>
<td>28</td>
</tr>
</tbody>
</table>

*there are missing data for ‘Not reported’ feeding type

A separate living systematic review has been commissioned by WHO to identify studies of mothers with suspected or confirmed COVID-19 whose breastmilk was tested for COVID-19. The review has not yet been published but a WHO scientific brief summarises the findings [121]. Evidence is derived from case series, case reports and family cluster reports.

Breastmilk samples were tested for 46 mothers with confirmed COVID-19. Although 13 infants had confirmed infection with COVID-19, only three samples tested positive for viral RNA particles by RT-PCR (not live virus). Of the three mothers with viral RNA particles in their breastmilk:

- 1 newborn was positive for COVID-19 (infection source unknown; feeding method not reported)
- 2 newborns were negative for COVID-19 (1 breastfed; 1 fed expressed breastmilk once viral RNA particles no longer detected)

The authors state that at present, data are not sufficient to conclude vertical transmission of COVID-19 through breastfeeding.
1. Number of infected newborns within 30 days of breastfeeding or receiving expressed breastmilk
2. Systematic review [119].

3. **Risk of bias:** **Very Serious.** Evidence is derived from case studies and case reports. **Inconsistency:** **Serious.** Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities. **Indirectness:** **Serious.** Differences between the outcomes of interest and those reported. Testing of breast milk not reported. **Imprecision:** **Serious.** Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities.

**Publication bias:** No serious.

<table>
<thead>
<tr>
<th>Number of infected newborns</th>
<th>Based on data from 666 patients in 49 studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within 30 days of exposure</strong></td>
<td>See summary for details. Included newborns who had confirmed postnatal infection of COVID-19 (28/666 newborns). Testing of breastmilk was not reported. Of the 28 newborns infected, seven were breastfed, three formula-fed and one was given expressed breastmilk. The method of feeding was not reported for 17 newborns.</td>
</tr>
<tr>
<td><strong>9 Critical</strong></td>
<td><strong>Very Low</strong> Due to very serious risk of bias, and serious imprecision, indirectness and inconsistency.</td>
</tr>
</tbody>
</table>

We are uncertain whether breastfeeding increases or decreases the number of infected newborns.
12 - Methods and Processes

For information about the methods and processes used please see the website. For the governance structure and details on members please also see the website.
13 - Conflicts of Interest

The policy for management of conflicts of interest and the template used for collecting the declarations of interest can be found on the website.

Declarations of interest will soon be made available on the website.
14 - Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs</td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>ANZICS</td>
<td>Australian and New Zealand Intensive Care Society</td>
</tr>
<tr>
<td>APO</td>
<td>Acute pulmonary oedema</td>
</tr>
<tr>
<td>ARBs</td>
<td>Angiotensin receptor blockers</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>BiPAP</td>
<td>Bilevel positive airway pressure (a form of oxygen therapy)</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus Disease 2019 (disease caused by the virus SARS-CoV-2)</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure (a form of oxygen therapy)</td>
</tr>
<tr>
<td>DMTs</td>
<td>Disease-modifying treatments</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation (a form of oxygen therapy)</td>
</tr>
<tr>
<td>FiO2</td>
<td>Fraction of inspired oxygen</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of recommendations, assessment, development, and evaluation</td>
</tr>
<tr>
<td>HCP</td>
<td>Healthcare professionals</td>
</tr>
<tr>
<td>HFNC</td>
<td>High-flow nasal cannula (a form of oxygen therapy)</td>
</tr>
<tr>
<td>HFNO</td>
<td>High-flow nasal oxygen (a form of oxygen therapy)</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IU</td>
<td>International units</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NMBAs</td>
<td>Neuromuscular blocking agents</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low-molecular-weight heparin</td>
</tr>
<tr>
<td>NIV</td>
<td>Non-invasive ventilation (a form of oxygen therapy)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>MERS</td>
<td>Middle East respiratory syndrome</td>
</tr>
<tr>
<td>PaO2</td>
<td>Partial pressure of arterial oxygen</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure (a form of oxygen therapy)</td>
</tr>
<tr>
<td>PPE</td>
<td>Personal protective equipment</td>
</tr>
<tr>
<td>RT-PCT</td>
<td>Reverse transcription-polymerase chain reaction</td>
</tr>
<tr>
<td>SARS</td>
<td>Severe acute respiratory syndrome</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe acute respiratory syndrome coronavirus 2 (the virus that causes the disease COVID-19)</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>VV ECMO</td>
<td>Venovenous extracorporeal membrane oxygenation (a form of oxygen therapy)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
References


[34] Hydroxychloroquine post-exposure prophylaxis for COVID-19.


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[44] Therapeutic Goods Administration : Australian Product Information: Xofluza (baloxavir marboxil) tablets. 2020; Website


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[66] Videolaryngoscopy versus Direct laryngoscopy for emergency intubation.


[70] Rombey T, Schieren M, Pieper D: Video versus direct laryngoscopy for inpatient emergency intubation in adults. Deutsches


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[83] NICE: COVID-19 rapid guideline: community-based care of patients with chronic obstructive pulmonary disease (COPD) [NG168]. 2020; Website

[84] NICE: COVID-19 rapid guideline: severe asthma [NG166]. 2020; Website

[85] Therapeutic Goods Administration: Australian Product Information: Dexamethsone (dexamethasone) tablets. 2018; Website


[90] Thrombosis and Haemostasis Society of Australia and New Zealand: Thromboprophylaxis and thrombosis in COVID-19 infected patients admitted to hospital. 2020; Website


[109] International Pharmaceutical Federation: FIP position statement on the association between the use of non-steroidal anti-inflammatory medicines (including ibuprofen), ACE inhibitors, angiotensin receptor blockers (ARBs) and corticosteroids, and an increased risk of coronavirus/COVID-19 infection or disease severity. 2020; [Website](https://www.ipf.org)

[110] Renal Association UK: Position statement on COVID-19 and ACE Inhibitor/Angiotensin Receptor Blocker use. 2020; [Website](https://www.renal.org)


[114] Canadian Cardiovascular Society: Guidance from the CCS COVID-19 rapid response team. 2020; [Website](https://www.ccs.ca)


[117] American Heart Association, Heart Failure Society of America and American College of Cardiology: Patients taking ACE-i and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician. 2020; [Website](https://www.ahajournals.org)


[122] Corticosteroids for COVID-19 with ARDS.