COVID-19 Treatment Guidelines for severe and critical disease (hospitalised Adults)

Department of Health

January 2022
COVID-19 Treatment Guidelines (Adults)
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About this document

This document has been developed by the Queensland Health COVID-19 Therapeutics Working Group to provide clinicians with recommendations on the treatment options for COVID-19 in adult and adolescent patients (>16 years). For guidance in the management of children with COVID-19, refer to the CHQ Paediatric Guideline.

These guidelines are based on the recommendations of the National COVID-19 Clinical Evidence Taskforce, the World Health Organisation (WHO) living guidelines, and the NIH (US) and NICE (UK) guidelines; they will be updated frequently as new evidence is made available.

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1. Classification of severity

Disease definitions according to by the Australian National COVID-19 Taskforce and World Health Organisation (WHO) living guidelines.

For patients with mild to moderate disease, see the COVID-19 Treatment Guidelines for mild-moderate disease (Adults).

1.1 Mild disease
- Patients with confirmed COVID-19 without evidence of viral pneumonia or hypoxia

1.2 Moderate disease
- Patients with confirmed COVID-19 with signs of pneumonia including SOB, tachypnoea, or cough without features of severe pneumonia (oxygen saturation ≥ 93% and <95% on room air (RA))
- Desaturation or breathlessness with mild exertion
- Imaging may be required to confirm the diagnosis of pneumonia

1.3 Severe disease
- Patients with confirmed COVID-19 with signs of severe pneumonia who is deteriorating
- Respiratory rate (RR) ≥ 30 breaths per minute
- Oxygen saturation ≤ 92% RA and/or requiring oxygen supplementation
- Lung infiltrates ≥ 50% on imaging

1.4 Critical COVID-19 infection
Defined as patients with respiratory tract infections progressing to respiratory failure, septic shock, or severe organ dysfunction
- Acute Respiratory Distress Syndrome (ARDS)
  - Onset usually within a week of respiratory symptoms
  - Bilateral opacities not explained by other aetiology
  - Oxygenation impairment (mild, moderate, or severe based on PaO₂/FiO₂)
- Life-threatening organ dysfunction/failure
- Impairment of consciousness
- Septic Shock
2. Treatment

2.1 Treatment principles

COVID-19 therapies other than those listed in this document should be prescribed only in the context of a clinical trial.

Do not combine immunomodulator therapies. **Additional dosing** of tocilizumab or extended courses of baricitinib or tofacitinib are not recommended.

Immunomodulator therapies should be used with caution for patients who are immunosuppressed.

Current standard of care therapy for patients with severe or critical disease may include:

1. Antiviral therapy (e.g., remdesivir)
2. Corticosteroids (dexamethasone, prednisolone, hydrocortisone)
3. Immune modulators (tocilizumab, baricitinib, tofacitinib).

Current evidence suggests that casirivimab plus imdevimab does not neutralise the omicron strain of the SARS-CoV-2 virus. It should not be used unless genotyping confirms infection with an alternate strain [1].

**Medication Access and Storage:**

Queensland health has centralised drug purchasing and storage which is managed via interconnected I Pharmacy Service with a rapid distribution process.

**Central pharmacy** coordinates the purchasing and procurement for all COVID-19 therapy. Sites can view the stock levels at Central Pharmacy and other QH pharmacies via the live dashboard [I Pharmacy State-wide - SOH and Usage - Power BI](#) accessed with Novell user name and password.

Sites are requested NOT to stockpile essential medicines and distribution will be limited to an estimated 24 hours of therapy, with allowance for distribution time across the state.
### 2.2 Overview of COVID-19 therapy

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe Disease</strong></td>
<td>• <strong>Dexamethasone</strong> should be used in all patients requiring oxygen therapy</td>
</tr>
<tr>
<td>(Patients with pneumonia requiring oxygen but not ventilation)</td>
<td>• Consider <strong>remdesivir</strong> in patients within 7 days of symptom onset for those requiring oxygen (but not ventilated)</td>
</tr>
<tr>
<td></td>
<td>• In patients with features of systemic inflammation*, consider one of:</td>
</tr>
<tr>
<td></td>
<td>o <strong>Baricitinib</strong> (or tofacitinib if baricitinib is unavailable)</td>
</tr>
<tr>
<td></td>
<td>o <strong>Tocilizumab</strong> (current stock levels in Australia remain low and therefore tocilizumab is not currently recommended unless the patient is pregnant)</td>
</tr>
<tr>
<td></td>
<td>• <strong>Casirivimab plus imdevimab</strong> is recommended in seronegative patients with moderate to critical COVID-19, who are not infected with Omicron strain [1]</td>
</tr>
<tr>
<td><strong>Critical Infection</strong></td>
<td>• <strong>Dexamethasone</strong> should be used in all patients requiring oxygen therapy</td>
</tr>
<tr>
<td>(Patients requiring ventilation)</td>
<td>• In patients with features of systemic inflammation* consider one of:</td>
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</tr>
</tbody>
</table>

*Systemic inflammation:

For **baricitinib** systemic inflammation is considered to be present if there are elevated levels of CRP, ferritin, LDH, or D-dimer.

For **tocilizumab** systemic inflammation is considered to be present if CRP > 75 mg/L.
3. Special considerations

3.1 Pregnancy

- **Do not use** baricitinib or tofacitinib in pregnant or breast-feeding women

- **Tocilizumab** may be used in pregnant women who require oxygen supplementation due to COVID-19 infection. Consider assessing initial response to corticosteroids first and use only if there are features of systemic inflammation such as CRP > 75 mg/L

- For pregnant women who are administered tocilizumab after 20 weeks gestation, avoid live vaccines for the newborn baby up to 6 months post-partum

- There is no need to avoid live vaccines in newborn babies who are breastfeeding if tocilizumab is administered post-partum

- Consider using remdesivir in hospitalised pregnant women with moderate or severe COVID-19 who do not require high flow oxygen or ventilation

4. Detailed COVID-19 therapies

4.1 Corticosteroids

Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen.[2, 3] This is thought to be by reducing the COVID-19-induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. For patients with COVID-19 who do not require supplemental oxygen, there is evidence that it may be associated with an increased risk of progression to invasive mechanical ventilation and death.

**Indications**

- Patients who require any supplemental oxygen to achieve prescribed oxygen saturation levels or patients who require supplemental oxygen but are unable to tolerate it (patients with severe or critical COVID-19 infection)

**Dose and duration**

- Dexamethasone (preferred): 6 mg orally or IV daily for up to 10 days. For some critically unwell patients in ICU, dexamethasone 12 mg IV daily may be appropriate

- Prednisolone (alternative): 50 mg orally daily for up to 10 days
• Hydrocortisone (alternative): 50 mg IV 6-hourly for up to 10 days

**Contraindications** – none

**Additional**

• Screen for opportunistic infections (see section 5, below)

### 4.2 Remdesivir

Remdesivir is a nucleotide prodrug of an adenosine analogue. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely.[4, 5] Remdesivir has demonstrated in vitro activity against SARS-CoV-2. Remdesivir is currently recommended by the Australian National Taskforce, NIH (US) and NICE (UK) guidelines. It is not recommended according to the WHO living guidelines. This discrepancy is due to the method of analysis applied to the current evidence whereby the Australian National COVID-19 Clinical Evidence Taskforce assessed according to disease severity classification. Remdesivir is not recommended for any ventilated patients with COVID-19 infection but may be continued if already administered prior to commencing ventilation. Remdesivir is currently available through the National Medical Stockpile (NMS) and criteria for use includes the need for oxygen therapy and limits the treatment course to 5 days for eligible patients.

**Indications**

• Severe COVID-19 pneumonia in patients who require oxygen (SpO2 ≤ 92% on room air) but do not require ventilation (invasive or non-invasive mechanical ventilation or ECMO)
• High risk for disease progression

**Note:** In the context of its current limited availability, remdesivir should be reserved for those patients most likely to benefit. Situations where patients should be prioritised include:

• Less than 7 days from onset of symptoms
• Not requiring high flow nasal oxygen
• Life expectancy greater than one year

**Contraindications**

• eGFR < 30 mL/min/1.73m²
• ALT/AST* ≥ 5 x upper limit of normal (ULN)
Dose and Duration

- Loading dose of 200 mg IV on day 1, then 100 mg IV daily on days 2-5 (maximum of 5 days)

Discontinue if

- ALT/AST* > 5 ULN during treatment, can restart when < 5 x ULN
- Other signs of liver inflammation (raised bilirubin, INR)
- eGFR < 30 mL/min/1.73m²

*ALT/AST: hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase.

4.4 Baricitinib

Baricitinib is a Janus Kinase (JAK) inhibitor that can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6).[6, 7] Baricitinib may also have antiviral activity by interfering with the SARS-CoV-2 virus entering and infecting potentially susceptible cells.

Indication

- Patients with severe or critical COVID-19 infection (including ventilated patients) with evidence of systemic inflammation (elevated CRP, D-Dimer, ferritin, LDH)
- Always use in combination with corticosteroids, consider assessing response to corticosteroids prior to commencing

Dose and Duration

- 4 mg orally^ ONCE DAILY for up to 14 days or until hospital discharge, whichever is soonest
- Dose is adjusted in renal impairment:
  - 2 mg orally ONCE daily for eGFR 30 – 60 mL/min/1.73m²
  - 1 mg orally ONCE daily for eGFR 15 – 30 mL/min/1.73m²
  - eGFR < 15 mL/min/1.73m² - NOT recommended
- Reduce dose to 2 mg orally ONCE daily if concurrently prescribed with probenecid

^Can be dispersed and given via nasogastric tube.
Contraindications

- Patients who are significantly immunosuppressed, due to additive risk of immunosuppression with baricitinib—however, in some patient groups (ie those who have undergone solid organ transplant) benefit may outweigh risk
- Do not combine with immunomodulating drugs other than corticosteroids
- Pregnancy or breastfeeding
- Use in caution for patients with high thrombotic risk such as current thrombosis or history of unprovoked thrombosis
- Use in caution for patients who have severe hepatic impairment. Note: clinical trials generally excluded patients with ALT/AST* > 5 x upper limit of normal

Additional

- Monitor for myelosuppression or LFT derangement
- Screen for opportunistic infections (see section 5)
- Monitor for Herpes simplex virus reactivation (clinical)

*ALT/AST: hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase.

4.5 Tofacitinib

If baricitinib is not available, tofacitinib may be an alternative because it has demonstrated clinical benefit in the STOP-COVID trial.[8] Note tofacitinib is not on the List of Approved Medicines in Queensland. Local individual patient approval (IPA) is required.

Indication

- **Note:** baricitinib is currently the preferred immunomodulating agent for COVID-19
- Tofacitinib is preferred for patients with renal impairment (eGFR < 15 mL/min/1.73m²), where baricitinib is contraindicated. See below for renally adjusted dose.
- Patients with severe or critical COVID-19 infection (including ventilated patients) with evidence of systemic inflammation (elevated CRP, D-Dimer, Ferritin, LDH)
- Always use in combination with corticosteroids, consider assessing response to corticosteroids first before commencing
Dose and Duration

- **10 mg orally TWICE DAILY** for up to 14 days or until hospital discharge, whichever is soonest
- eGFR < 30 mL/min/1.73m² (including haemodialysis): 5 mg orally TWICE daily

Contraindications

- Patients who are significantly immunosuppressed, due to additive risk of immunosuppression with tofacitinib—however, in some patient groups (ie those who have undergone solid organ transplant) benefit may outweigh risk
- Do not combine with immunomodulating drugs other than corticosteroids
- Pregnancy or breastfeeding
- Use in caution for patients with high thrombotic risk such as current thrombosis or history of unprovoked thrombosis
- Use in caution for patients who have severe hepatic impairment. Note: clinical trials generally excluded patients with ALT/AST > 5 x upper limit of normal

Additional

- Monitor for myelosuppression or LFT derangement
- Screen for opportunistic infections ([see section 5](#))
- Monitor for *Herpes simplex* virus reactivation (clinical)

4.6 Tocilizumab

The results of the RECOVERY and REMAP-CAP trials demonstrated that tocilizumab, when co-administered with corticosteroids, offers a modest mortality benefit in certain patients with COVID-19 who are severely ill, who are rapidly deteriorating and have increasing oxygen needs, and who have a significant inflammatory response.[9, 10] In patients who are receiving supplemental oxygen, baricitinib should be considered as an alternative to tocilizumab.

Indications

- Baricitinib is the preferred immunomodulating agent for COVID-19 currently
- Always use in combination with corticosteroids, consider assessing response to corticosteroids first before commencing
- Hospitalized patients with severe or critical COVID-19 with CRP ≥ 75 mg/L
• Can be considered in pregnant or breastfeeding women particularly when there is
evidence of systemic inflammation

• Tocilizumab supply chain is currently constrained, and stock is very limited. Reserve
this agent for pregnant or breastfeeding women. Tofacitinib is preferred for patients
with eGFR < 15 mL/min/1.73m²

**Dose and Duration**

• Dose according to actual body weight (capped at 800 mg)

<table>
<thead>
<tr>
<th>Patient weight</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 90 kg</td>
<td>800 mg</td>
</tr>
<tr>
<td>&gt; 65 kg and ≤ 90 kg</td>
<td>600 mg</td>
</tr>
<tr>
<td>&gt; 40 kg and ≤ 65 kg</td>
<td>400 mg</td>
</tr>
<tr>
<td>≤ 40 kg</td>
<td>8 mg/kg</td>
</tr>
</tbody>
</table>

• Administer as a single intravenous infusion over 60 minutes.

**Contraindications**

• ALT or AST > 5 x upper limit of normal

• Patients who are significantly immunosuppressed, due to additive risk of
immunosuppression with tocilizumab—however, in some patient groups (i.e., those
who have undergone solid organ transplant) benefit may outweigh risk

• Absolute neutrophil counts < 500 cells/µL

• Platelet counts < 50 000 cells/µL

• Do not combine with immunomodulating drugs other than corticosteroids

**Additional**

• Monitor for myelosuppression or LFT derangement

• Screen for opportunistic infections

• Monitor for *Herpes simplex* virus reactivation (clinical)

• Tocilizumab inhibits CRP so a reduction in CRP cannot be used as a marker of clinical
improvement

4.9 Casirivimab/imdevimab (Ronapreve®) High dose
High dose casirivimab/imdevimab was shown to reduce mortality for hospitalised patients with COVID-19 infection who are seronegative. In seronegative patients treated with casirivimab/imdevimab there was a significant reduction in mortality compared to standard of care (NNT approximately 20).[11]

**NOTE:** Current evidence suggests that casirivimab/imdevimab does not neutralise the Omicron strain of the SARS-CoV-2 virus. It should not be used unless genotyping confirms infection with an alternate strain[1]

### Indications
- Severe or critical COVID-19 admitted patients who do not have an anti-COVID-19 IgG antibody detected within 24 hours of administration (request “urgent COVID-19 serology COVGQ” to Pathology Queensland)

### Dose and duration
- Single combined dose of **1200 mg casirivimab and 1200 mg imdevimab** given by intravenous infusion over 30 minutes

### Contraindications
- Known reactions to prior monoclonal antibodies
- Avoid in pregnant women in their first trimester

### 5. Opportunistic infections

#### 5.1 Screening

The following investigations should be performed on moderate, severe, or critical COVID-19 patients on admission to hospital. For mild COVID-19 patients, clinical judgement should apply based on the risk of progression.

- HBV serology (HBsAg, HBsAb, and HBsAb)
- Strongyloides serology
- HIV serology
- HCV serology
- TB QuantiFERON Gold
- Consider stool collection for culture in individuals at high risk of Strongyloides infection.
5.2 Tuberculosis

Patients with a positive QuantiFERON TB Test should be assessed for evidence of active tuberculosis on the basis of history, examination, CXR +/- CT findings. Latent TB therapy should be directed by an infectious diseases physician or respiratory physician.

5.3 Strongyloides

If a patient has a positive Strongyloides serology or detection on stool microscopy, prescribe:

- Ivermectin 200 mcg/kg (rounded up to the nearest 1.5 mg) orally, once daily, to be taken with fatty food on days 1, 2, 15 and 16. Ivermectin should not be given during pregnancy or to children who are aged < 5 years and/or who weigh < 15 kg. Albendazole may be an alternative, discuss with Infectious Diseases specialist.

5.4 Hepatitis B virus

All HBsAg positive patients must have HBV-DNA blood test performed to determine disease activity. If a patient receives dexamethasone, baricitinib, tofacitinib, tocilizumab or sarilumab and is HBsAg positive OR anti-HBc positive consider commencing entecavir (commence tenofovir if pregnant). This decision should be made in consultation with the local hepatology service where possible. Entecavir should be continued for 6 months post discharge.

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50 mL/min</td>
<td>0.5 mg oral daily</td>
</tr>
<tr>
<td>≥ 30 – 49 mL/min</td>
<td>0.5 mg oral second daily</td>
</tr>
<tr>
<td>≥ 10 – 29 mL/min</td>
<td>0.5 mg oral third daily</td>
</tr>
<tr>
<td>&lt; 10 mL/min (or dialysis dependant)</td>
<td>0.5 mg every 7 days (post dialysis)</td>
</tr>
</tbody>
</table>

Note: Entecavir is contraindicated in pregnancy or where there is a risk of pregnancy occurring. Use tenofovir 300mg orally daily in these circumstances. Administration interval adjustment for renal impairment is the same for tenofovir as for Entecavir.

Patients who are commenced on HBV treatment require appropriate follow up with a Hepatitis B specialist and to have a liver USS performed prior to their appointment. The liver
USS can be performed as an outpatient once the patient has completed their isolation period.

5.5 Hepatitis C virus

There is no prophylaxis for patients infected with HCV, but all anti-HCV positive patients need to have HCV-RNA blood test performed and subsequent appropriate referral to a Hepatitis C specialist. Patients who are referred to hepatology OPD should have hepatitis C genotype and liver USS performed prior to their appointment. The liver USS can be performed as an outpatient once the patient has completed their isolation period.

6. References

### 7. Version control

<table>
<thead>
<tr>
<th>Version</th>
<th>Amendments</th>
<th>Author/s</th>
<th>Approved for Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>v 1-0</td>
<td>New document</td>
<td>Andrew Henderson</td>
<td>23/12/2021</td>
</tr>
<tr>
<td>v 1-0</td>
<td>Endorsed</td>
<td>COVID System Response Group</td>
<td>11/01/2022</td>
</tr>
</tbody>
</table>
| v 1-1   | Amendments:  
  s4.2 Remdesivir – addition of advice around prioritising treatment in context of constrained supply  
  s4.7 Tofacitinib – statement added to preference tofacitinib over tocilizumab for patients with severe renal impairment.  
  s4.8 Tocilizumab – addition of advice to reserve for pregnant women in context of limited supply, tofacitinib preferred in non-pregnant patients with severe renal impairment.  
  Removal of the word “asymptomatic” in reference to indications for sotrovimab and casirivimab/imdevimab. | Andrew Henderson | 18/01/2022 |
| V1-2    | Amendments  
  Title – document renamed from COVID-19 Treatment Guidelines (Adults) to COVID-19 Treatment Guidelines for severe and critical disease (hospitalised adults)  
  s1.0 Link added to new COVID-19 Treatment Guidelines for mild to moderate disease.  
  s2.2 Table updated to remove rows related to therapies for mild and moderate disease.  
  s4.1 updated corticosteroid doses to align with National Living Guideline  
  s5.3 added information about ivermectin dosing and pregnancy and children  
  s4.1, s4.5, s4.6 clarified contraindication to baricitinib, tocilizumab and tofacitinib in immunosuppressed patients.  
  s4.7, s4.9 and s4.10 regarding treatments for mild-moderate disease removed. | Amy Legg  
Tina Patterson  
Andrew Henderson | 1/03/2022 |