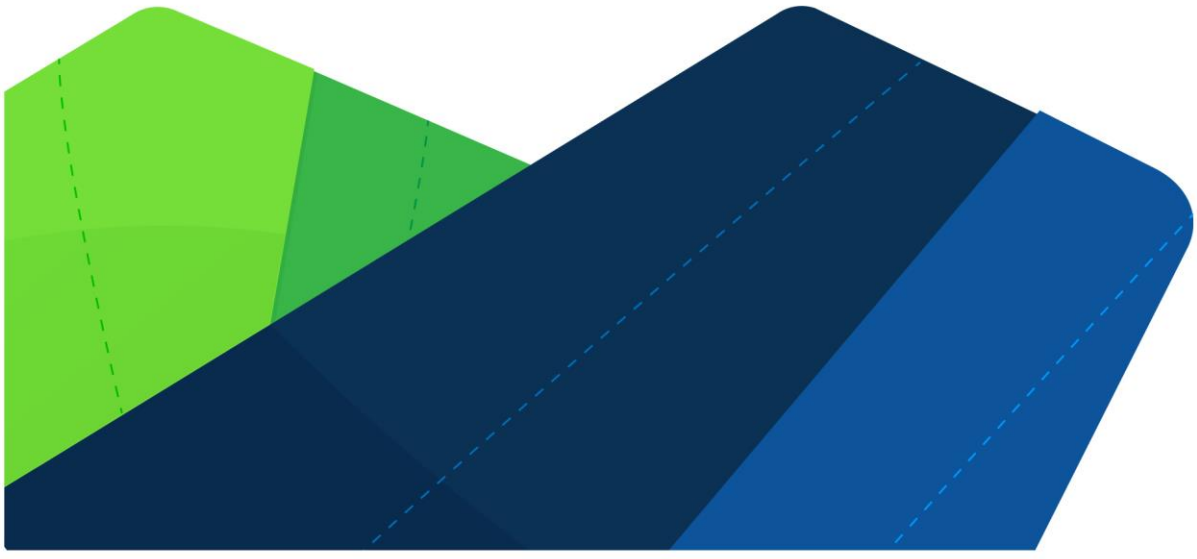
COVID-19 Treatment Guidelines (Adults)

Department of Health

January 2022



Queensland Government

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.

Table of Contents

1. Classification of severity

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

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 PaO_2/FiO_2)
- Life-threatening organ dysfunction/failure
- Impairment of consciousness
- Septic Shock
    - Sepsis with persistent hypotension despite volume resuscitation

2. Treatment

2.1 Treatment principles

COVID-19 therapy other than what is listed in this document specifically for treatment of COVID-19 infection should be prescribed only in the context of a clinical trial.

Do not combine immunomodulator therapies for patients.

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 moderate, severe, or critical disease may include:

1. Antiviral therapy (remdesivir)
2. Corticosteroids (dexamethasone/prednisolone/hydrocortisone)
3. Immune modulators (tocilizumab/baricitinib/tofacitinib)
4. Monoclonal antibodies (sotrovimab, casirivimab plus imdevimab)

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

Disease Severity	Therapeutic options
Mild Disease *Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. These patients are not on O_2 therapy*	• **Sotrovimab** should be offered to patients within 5 days of symptom onset who are not fully vaccinated to COVID-19 and who have medical conditions associated with risk of progression to severe infection or who are immunosuppressed regardless of vaccination status. • **Casirivimab/imdevimab** may be used as an alternative to **sotrovimab** for patients with symptom onset between 5-7 days for patients who **are not infected by the Omicron strain[1]** • Consider inhaled **budesonide** in non-hospitalised patients within 14 days of symptom onset at risk of disease progression. (Current availability of budesonide is limited, and the effect of budesonide is uncertain on disease progression and mortality. Each facility should assess the availability and potential benefit in forming local practice)
Moderate Disease (Patients with pneumonia not requiring oxygen) *Clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥ 93% on room air. These patients are not on O_2 therapy.*	• **Sotrovimab** should be offered to patients within 5 days of symptom onset who are not fully vaccinated to COVID-19 and who have medical conditions associated with risk of progression to severe infection or who are immunosuppressed regardless of vaccination status. • **Casirivimab/imdevimab** may be used as an alternative to **sotrovimab** for patients with symptom onset between 5-7 days for patients who **are not infected by the Omicron strain[1]** • Consider inhaled **budesonide** in non-hospitalised patients within 14 days of symptom onset, who are at risk of disease progression. (Current availability of budesonide is limited, and the effect of budesonide is uncertain on disease

	progression and mortality. Each facility should assess the availability and potential benefit in forming local practice)
Severe Disease (Patients with pneumonia requiring oxygen but not ventilation) *Clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO_2 < 93% on room air.*	• **Dexamethasone** should be used in all patients requiring oxygen therapy • Consider **remdesivir** in patients within 10 days of symptom onset • Consider **high dose casirivimab/imdevimab** in patients who are not immune to COVID-19 (IgG negative) and who **are not infected by the Omicron strain[1]** • In patients with features of systemic inflammation* consider one of: ○ **Baricitinib** (or tofacitinib if baricitinib is unavailable) ○ **Tocilizumab** (current stock levels in Australia remain low and therefore tocilizumab is not currently recommended unless the patient is pregnant)
Critical Infection (Patients requiring ventilation) *Critical disease: Acute respiratory distress syndrome with PaO_2:FiO_2 ratio of < 200*	• **Dexamethasone** should be used in all patients requiring oxygen therapy • Consider **high dose casirivimab/imdevimab** in patients who are not immune to COVID-19 (IgG negative) and who **are not infected by the Omicron strain[1]** • In patients with features of systemic inflammation* consider one of: ○ **Baricitinib** (or tofacitinib if baricitinib is unavailable) ○ **Tocilizumab** (current stock levels in Australia remain low and therefore tocilizumab is not currently recommended unless the patient is pregnant)

*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.

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
- 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

3.4 Impaired kidney function

3.2 Post-exposure prophylaxis (PEP)

- **Casirivimab/imdevimab** is approved for post-exposure prophylaxis for close contacts (weighing over 40 kg) who are at high risk for progression to severe COVID-19 and who are not fully vaccinated or who are not expected to respond to vaccination)
- At present there is limited availability of casirivimab/imdevimab for post-exposure prophylaxis, therefore PEP should primarily be reserved for close contacts exposed in high risk settings such as hospitals or residential aged care facilities.
- The recommended PEP dose is 600mg/600mg within 4 days of exposure.
- **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]**

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 daily** or **8 mg IV daily** for 10 days
- Prednisolone (alternative): 40 mg orally daily for 10 days
- Hydrocortisone (alternative): 50 mg IV daily Q8H for 10 days
- May be continued for up to 28 days in patients with septic shock

Contraindications – none

Additional

- Screen for latent 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/1.73m^2
- 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/1.73m^2

*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/1.73m^2
    - 1 mg orally ONCE daily for eGFR 15 – 30 mL/min/1.73m^2
    - eGFR < 15 mL/min/1.73m^2 - NOT recommended

^Can be dispersed and given via nasogastric tube.

Contraindications

- Patients who are significantly immunosuppressed, particularly in those with recent use of other biologic immunomodulating drugs
- 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 latent 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]

Indication

- Note: baricitinib is the preferred immunomodulating agent for COVID-19 currently
- Tofacitinib is preferred for patients with renal impairment (eGFR < 15 mL /min/1.73m^2), 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/1.73m^2 (including haemodialysis): 5 mg TWICE daily

Contraindications

- Patients who are significantly immunosuppressed, particularly in those with recent use of other biologic immunomodulating drugs
- 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 latent 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
- 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/1.73m^2

Dose and Duration

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

Patient weight	Dose
> 90 kg	800 mg
> 65 kg and ≤ 90 kg	600 mg
> 40 kg and ≤ 65 kg	400 mg
≤ 40 kg	8 mg/kg

- Administer as a single intravenous infusion over 60 minutes.

Contraindications

- ALT or AST > 5 x upper limit of normal
- Patients who are significantly immunosuppressed, particularly in those with recent use of other biologic immunomodulating drugs
- 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 latent opportunistic infections
- Monitor for *Herpes simplex* virus reactivation (clinical)

4.7 Sotrovimab

Sotrovimab is a recombinant human immunoglobulin monoclonal antibody targeting the spike protein receptor binding domain of SARS-CoV-2. The COMET-ICE trial demonstrated efficacy and safety data in 291 patients in the sotrovimab treatment arm.[11] A single 500 mg infusion of sotrovimab was found to decrease the risk of hospitalisation if given within 5 days of symptom onset in non-hospitalised, partially or unvaccinated patients with confirmed COVID-19 who did not require oxygen and were at high risk of medical complications compared to placebo. The number needed to treat with sotrovimab to prevent one hospitalisation event is approximately 16.

Indications

- mild, or moderate COVID-19 not requiring oxygen
- Non-hospitalised patients
    - Have not received 2 vaccine doses (> 2 weeks or who have not developed an antibody response) AND are at risk of progressing to severe disease and hospitalisation OR are immunosuppressed* regardless of vaccine status
- Hospitalised patients
    - Not admitted for primary management of COVID-19 symptoms who meet the criteria for non-hospitalised patients

- Should be commenced as soon as possible after the patient has a positive result and within 5 days of symptom onset

Dosage and duration

- Give **500 mg as a single dose** intravenous infusion over 30 minutes
- Should only be administered in an appropriate healthcare setting with patients monitored for the duration of the infusion and for 60 minutes after the infusion ends.

Contraindications

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

4.8 Casirivimab/imdevimab (Ronapreve®) Standard dose

Casirivimab/imdevimab is a recombinant human immunoglobulin monoclonal antibody combination targeting two distinct sites on the spike protein receptor binding domain of SARS-CoV-2. It may be used as an alternative to sotrovimab, particularly those at day 5 – 7 from symptom onset. Sotrovimab is the preferred agent due to drug availability, ease of administration and activity against the Omicron strain. The REGEN-COV study demonstrated efficacy of both 600mg/600mg and 1200mg/1200mg doses with an overall 2.2% absolute reduction and 70% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths.[12]

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

- Mild or moderate COVID-19 not requiring oxygen
- Non-hospitalised patients
    - Have not received 2 vaccine doses (> 2 weeks or who have not developed an antibody response) **AND** are at risk of progressing to severe disease and hospitalisation **OR** are immunosuppressed* regardless of vaccine status
- Hospitalised patients
    - Not admitted for primary management of COVID-19 symptoms who meet the criteria for non-hospitalised patients

- Should be commenced as soon as possible after the patient has a positive result and **within** 7 days of symptom onset

Note: sotrovimab is the preferred monoclonal antibody therapy for non-hospitalised patients at risk of disease progression. Casirivimab/imdevimab may be considered for patients between day 5 – 7 of symptom onset.

Dose and duration

- Single combined dose of **600 mg casirivimab and 600 mg imdevimab** given by intravenous infusion over 30 minutes
- Should only be administered in healthcare settings with patients monitored for the duration of the infusion and for 60 minutes after the end of the infusion.
- Casirivimab/imdevimab can be given by subcutaneous injection, however this requires the administration of four separate injections given consecutively and should be reserved when there is no intravenous access. The same monitoring requirements apply.

Contraindications

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

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).[13]

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 **1 200 mg casirivimab and 1 200 mg** imdevimab given by intravenous infusion over 30 minutes

Contraindications

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

4.10 Budesonide (inhaled)

Budesonide currently has a conditional recommendation by the Australian National COVID-19 Taskforce. It is not recommended in the NICE Guidelines (UK) or NIH Guidelines (US) outside of a clinical trial. There is significant uncertainty over current clinical benefit and extremely limited access in Queensland.[14]

Indications

- Mild or moderate COVID-19 patients who do not require oxygen supplementation with risk factors for disease progression:
    - Diabetes (not treated with insulin)
    - Heart disease and/or hypertension
    - Asthma or lung disease
    - Weakened immune system due to a serious illness or medication (e.g. chemotherapy)
    - Mild hepatic impairment
    - Stroke or other neurological problem

Dose and duration

- **2 puffs (400 µg) TWICE DAILY** until symptom resolution

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 adding stool collection for Strongyloides 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 stool test, prescribe:

- **Ivermectin 200 mcg/kg** to be taken with fatty food on days 1, 2, 15 and 16.

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.

Creatinine clearance	Dose
≥ 50 mL/min	0.5 mg oral daily
≥ 30 – 49 mL/min	0.5 mg oral second daily
≥ 10 – 29 mL/min	0.5 mg oral third daily
< 10 mL/min (or dialysis dependant)	0.5 mg every 7 days (post dialysis)

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.

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7. Version control

Version	Amendments	Author/s	Approved
v 1-0	New document	Andrew Henderson	23/12/2021
v 1-0	Endorsed	COVID System Response Group	11/01/2022
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 Endorsed: Keith McNeil A/Deputy Director-General, CMO and CCIO, Prevention Division	18/01/2022