	Pregnancy (meeting the same clinical criteria as above)	• Avoid remdesivir in <12/40 gestation • Use remdesivir if >12/40 gestation as per Adult Guideline indications with the same dosing as above • Remdesivir is compatible with breastfeeding
IMMUNE MODULATION THERAPY	**In patients receiving systemic steroids in combination with immune modulation, we recommend screening for, and consider empiric treatment of latent infection, e.g. Hepatitis B or strongyloidiasis (in patients who have lived in an endemic region)**	
	There are no trials of immune modulation therapies currently recruiting in New Zealand	
	Adults with moderate COVID-19 • AND receiving systemic steroids • AND elevated CRP or other evidence of severe systemic inflammation OR clinically deteriorating • AND there is not another active, severe concurrent infection	Give tocilizumab: • 8mg/kg IV (actual body weight) rounded to nearest 200mg (max dose 800mg), as a single dose • *Notes: risk of secondary infection may be increased; CRP response is inhibited, and consequent reduction in CRP does not necessarily correlate with response to treatment* OR baricitinib: • 4mg PO/NG daily for 14 days or until hospital discharge • Reduce to 2mg PO daily if eGFR 30-60mL/min • Reduce to 1mg PO daily if eGFR 15-29mL/min • Do not use if eGFR <15mL/min • Avoid in pregnancy or breastfeeding • Baricitinib is a **section 29** product
	Adults with severe / critical COVID-19 requiring mechanical ventilation or organ support: • AND receiving systemic steroids • AND there is not another active, severe secondary infection • As soon as possible (ideally within 24 hours) of starting HFNO, NIV, mechanical ventilation or organ support	Give tocilizumab as above Baricitinib may be considered as an alternative to tocilizumab if unavailable (as above) If baricitinib commenced earlier in illness: • Continue the planned course as above • Do not add tocilizumab • If enteral route compromised, discuss potential switch with Infectious Diseases as soon as possible
	COVID-19 not meeting the criteria above	Do not use immune modulation therapy
	Pregnancy (meeting the same clinical criteria as above)	Give tocilizumab (same dosing as above): • *Notes: Tocilizumab crosses the placenta after 28/40, but no evidence of harm to date. Suggest deferring live vaccination (i.e. Rotarix, BCG) up to 6 months in neonates with antenatal exposure. All other vaccinations are safe.* • *Compatible with breastfeeding.* • *May cause raised ALT and thrombocytopenia, mimicking pre-eclampsia / HELLP.* • *Do not use baricitinib (as above)*

Discharge Planning and Follow-up

Patients with Suspected, Probable or Confirmed COVID-19 who are being considered for discharge need to have specific decisions made about the following aspects of post-discharge care:

FURTHER INVESTIGATIONS	• Follow-up investigations are not universally required after COVID-19 • A repeat chest x-ray in 6-12 weeks to confirm resolution of pulmonary opacities should be arranged for individuals with significant radiographic abnormalities and / or risk factors for lung cancer • Ensure follow up serology is arranged for 'probable' cases	
DISCHARGE DESTINATION	• Suspected cases being discharged before results are available should be notified to local Medical Officer of Health, who may request discharge to a quarantine facility • Decision about ability to safely isolate in usual place of residence needs to be assessed prior to discharge. If not able to safely complete isolation period in usual place of residence, should be referred for isolation in managed isolation facility, according to local referral pathways	
CLEARANCE FROM ISOLATION	• The decision to end isolation should be consistent with Public Health policies • In general, the principles that influence duration of isolation include: severity of COVID-19 illness, presence of significant immunocompromise, vaccination status and stable or improving symptoms prior to clearance	
FOLLOW-UP	All patients	• Telephone follow-up within 6 weeks of discharge with Primary Care Provider: to assess trajectory of recovery, identify persistent symptoms and facilitate referral to specialty services as required • Encourage vaccination if not fully vaccinated. Vaccination is recommended from 4 weeks after clinical recovery. If a patient has received either anti-spike monoclonal antibodies or convalescent plasma delay vaccination until at least 90 days after treatment
	Patients with significant respiratory failure (and/or persistent dyspnoea) or other persistent organ dysfunction	Specialist clinic follow-up, investigations and support following discharge (as advised by local specialty services)
	Patients discharged with nocturnal CPAP (usual OR new device)	Consider providing a non-vented mask + expiratory port + filter if discharging to MIQ (depending on equipment availability and staff expertise). Sleep service remote follow-up within 48 hours of hospital discharge is recommended if non-vented mask set up is used. Can transition to vented mask on return to own home.
	Pregnancy (or recently post-partum)	• VTE prophylaxis - refer to specific guidelines above • Recommend follow up growth scan within 2 weeks • If possible, delay follow-up CXR until post-partum

Links to other guidelines

- **Australian COVID-19 living guidelines:** https://covid19evidence.net.au/
- **NICE (UK) living guideline:** https://www.nice.org.uk/guidance/ng191
- **National Institute of Health (USA):** https://www.covid19treatmentguidelines.nih.gov/
- **WHO COVID-19 living guideline:** https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3
- **Ontario COVID-19 Science Advisory Group guideline (Canada) :** https://covid19-sciencetable.ca/sciencebrief/clinical-practice-guideline-summary-recommended-drugs-and-biologics-in-adult-patients-with-covid-19-version-5-0/
- **Australian guidance for Pregnancy and perinatal care:** https://covid19evidence.net.au/

Clinical Management of COVID-19 in Hospitalised Adults (including in pregnancy)

Introduction

Updated 4 March 2022 – Next planned update 1 April 2022 (NB additional updates anticipated prior to this date)

- Separation of COVID-19 therapeutic recommendations for patients with and without oxygen requirement
- Addition of prioritisation framework for patients without oxygen requirement at higher risk of severe disease
- Addition of recommendation to consider use of remdesivir in hospitalised adults not requiring oxygen and at high risk of developing severe disease
- Removal of conditional recommendation to consider remdesivir for moderate hospitalised patients requiring oxygen within the first week of illness
- Removal of casivirimab/imdevimab (Ronapreve) from recommended COVID-19 therapeutics
- Amendment of recommended groups in whom to consider budesonide
- Addition of consideration to give a higher dose of dexamethasone for patients who qualify for immunomodulatory therapy, but medication is not available
- Addition of recommendation to consider other concurrent diagnoses in vaccinated patients presenting with Omicron variant infection
- Amendment of respiratory support section to recommend CPAP as preferred treatment for patients with a requiring more than 40% oxygen.
- Addition of suggestion to consider vaccination status and number and severity of comorbidities during risk assessment
- Change from mandatory to 'consider' for D-dimer and ferritin in patients with moderate illnesss
- Removal of guidance for evaluating 'suspected' COVID-19 with serology
- Removal of routine recommendation to continue anticoagulation after discharge for pregnancy
- Recommendation to consider individual factors influencing risk of deterioration, including vaccination status, Omicron variant, age and number and severity of high-risk comorbidities.
- Removal of requirement to delay vaccination by 90 days after anti-SARS-CoV-2 antibody therapy
- Updated discharge and clearance from isolation recommendations in line with current public health guidance

New content in this update is highlighted in red.

This guideline is intended to be an accessible summary of hospital management of **ADULTS** (including in pregnancy**)** with **confirmed or probable COVID-19**. It has been adapted from international 'living' guidelines for the New Zealand context by an advisory group of New Zealand clinicians, including representation from Infectious Diseases, Respiratory Medicine, Intensive Care, General Medicine, Obstetric Medicine, Primary Care, Emergency Medicine and Pharmacy.

New evidence informing the optimal management of patients with COVID-19 continues to accumulate rapidly. This document will be reviewed and updated periodically, or in response to significant changes in evidence and/or recommendations by international guideline groups.

Further detailed guidance, including treatments that are either not recommended, or recommended only within a clinical trial, can be accessed in links to international guidance at the end of this document. Local specialist services with expertise in managing COVID-19 may consider emerging treatments outside of this guideline.

Additional details or differences on managing a pregnant woman are highlighted in orange rows just below the adult guidance.

Initial Management

	MILD	MODERATE	SEVERE / CRITICAL
DEFINITION	No symptoms **OR** URTI symptoms only **OR** cough, new myalgia or asthenia <u>without</u> new shortness of breath or reduction in resting oxygen saturation	Stable adult patient presenting with shortness of breath and/or reduction in resting oxygen saturation while breathing air. Able to maintain oxygen saturation ≥92% (or ≥90% for patients with chronic lung disease) with up to 4 L/min oxygen via nasal prongs	Adult patients meeting any of the following criteria: • Respiratory rate ≥30/min • Oxygen saturation <92% on 4L/min oxygen via nasal prongs • Clinically deteriorating
	Pregnancy: use an oxygen saturation **target of ≥ 94%** rather than ≥92%		
BASELINE TESTING & WORK-UP	• Pulse oximetry • Other tests only as clinically indicated • Low value testing is discouraged	• FBC, Creat, electrolytes, LFTs, CRP • ECG only if specific indication • Chest x-ray • Venous blood gas (consider arterial) • Investigations for CAP (e.g. urinary antigens, sputum PCR panel) if radiography suggests **bacterial infection** • Consider **d-dimer & ferritin**	• FBC, Creat, electrolytes, LFTs, CRP • ECG • Chest x-ray • Venous blood gas (consider arterial) • Investigations for CAP (e.g. urinary antigens, sputum PCR panel) if radiography suggests **bacterial infection** • Blood cultures if febrile or shocked • Coag screen, d-dimer, ferritin, BNP, Troponin
	• Note – in vaccinated individuals with Omicron variant infection, COVID-19 may not be the primary diagnosis responsible for hospital presentation. It is important to consider concurrent non-COVID-19 medical conditions during evaluation.		

	• **Pregnancy:** also request urine protein:creatinine ratio, coagulation profile, group and screen (or cross match if delivery is thought to be imminent) • *NB* CXR and CT chest / CTPA can safely be performed in pregnancy if clinically indicated. • Laboratory results should be cautiously interpreted, using pregnancy-specific ranges where available. There are no validated pregnancy-specific values for D-dimer; consider monitoring trend for prognostic purposes in severe/deteriorating COVID-19.		
TREATMENT ESCALATION PLANNING	• Assess ability to safely isolate in community. • Notify and refer through local pathways • Consider & document risk factors for severe COVID-19	• Assess & document individual **risk factors for poor outcome** • Early discussion of patient goals of care, including existing advanced care plans, with patient and their family/whānau • Early, clear documentation of resuscitation decision and treatment escalation plan for <u>all</u> patients, specifically including appropriate modalities of respiratory support	
	• **NOTE – any new deterioration > 5 days post onset of illness requires careful assessment, observation & judgement. Severe COVID-19 frequently develops with a rapid deterioration**		
	• For pregnant and post-partum observations, utilise a maternity-specific chart (if available) • Recommend early consultation with Obstetrics, Anaesthesia and NICU (and Obstetric Physician if available)		
DISPOSITION DECISION	• Encourage **discharge** • Liaise with local Public Health Unit or Regional Isolation and Quarantine (RIQ) according to regional processes	• Discuss with local COVID team • Admit to hospital if **Sa02 <93%** • Consider discharge if Sa02 ≥93% according to local protocols and availability of acute community COVID-19 care (e.g. primary care or hospital in the home service)	• Admit to hospital • ICU and/or Respiratory review
MONITORING & MARKERS OF CLINICAL DETER ORATION	• Risk of deterioration is signif cantly reduced by vaccination and infection with Omicron variant. Individualised risk assessment should include consideration of vaccination status, day of illness, age, immunocomromise and comorbidities that **increase risk of severe disease**. • Ferritin and d-dimer are suggested as severity/prognosis markers, as part of an overall assessment • Monitor for progressive respiratory failure and sepsis, especially after day 5 of illness • Only repeat CXR during admission for confirmed COVID-19 for specific clinical indications • Perform a chest CT scan only if it would change management, in particular if concern for pulmonary embolism • Anticipate complications such as delirium, pulmonary embolism, other thromboembolism, arrhythmias, cardiac impairment, acute kidney injury, sepsis, shock and multi-organ dysfunction, and address using existing standards of care. Also be aware of potential medication complications • Repeat **baseline investigations** periodically in patients who are not clearly improving, in order to detect & manage the above complications		
	Additional considerations in pregnancy: • Screen for pre-eclampsia in all pregnancies > 20/40 gestation and review at each assessment: i.e., systolic BP <u>></u> 140mmHg and/or diastolic <u>></u> 90, worsening peripheral oedema, headache, visual changes or upper abdominal pain. Risk of pre-eclampsia is increased in COVID-19. • Consider repeating laboratory investigations if there is a change in maternal condition • Appropriateness and frequency of fetal heart rate monitoring and ultrasound to be considered on individual basis, accounting for gestational age and clinical severity. Consider parameters for delivery (in discussion with neonatologists, anaesthetists ± intensive care team) • Consider steroids for the fetal lung maturation, and magnesium sulphate for neuroprotection or severe pre-eclampsia as per local obstetric guidelines • Consider emergency delivery if required for maternal resuscitation (including need for prone positioning) or for immediate fetal concern		

NOTIFICATION	• Discuss all cases with local COVID team at the earliest opportunity, according to local protocols • If not already notified according to regional process, (e.g. by laboratory) contact local Public Health Unit
	• If hospitalised, all pregnant women should have multidisciplinary assessment by obstetricians, midwives, neonatologists +/- an obstetric physician at the earliest opportunity • Recommend notification of all antenatal and postnatal cases to New Zealand Registry of COVID-19 in Pregnancy
CLINICAL TRIALS	• As the optimal management of COVID-19 is not yet known, the **standard of care is to be offered enrolment in a clinical trial,** if available • **All** patients should be screened for eligibility for a locally available COVID-19 clinical trial (e.g. 'REMAP-CAP' and 'ASCOT-ADAPT')

Supportive Management

MODALITY	PATIENT SUB-GROUPS	RECOMMENDATION
RESPIRATORY SUPPORT	All patients	• Switch nebulisers to metered dose inhalers via spacer if possible • Monitor closely for worsening hypoxia if elevated work of breathing or respiratory rate
	SpO_2 <92% at rest	• Administer dry oxygen (1-4 L/min) via standard nasal prongs • Use Hudson mask (5-10 L/min), Venturi device or high flow nasal oxygen (HFNO) if required • Aim for SpO_2 92–96% (88–92% for those at risk of hypercapnic respiratory failure) • Encourage use of self-proning
	Unable to maintain SpO2 ≥92% on conventional oxygen or high flow nasal oxygen [HFNO] (requiring Fi02 >40%)	• Consider CPAP. Settings should be individualised, but a starting pressure of 8-10cm H_20 is common • Continue HFNO if CPAP unavailable, during meal breaks from CPAP or patient intolerance of CPAP • Encourage use of self-proning
	Hypercapnic patients with underlying COPD or OHS	• Consider BiLevel Non-Invasive Ventilation (NIV) in addition to above
	Pregnancy	• SpO2 target is ≥ 94%; ideally aim for 96-98%. • After 20/40 avoid positioning flat on back: use a wedge for lateral supine positioning. Left lateral during resuscitation or if hypotensive. • Self-proning may be possible (depending on gestation and habitus).
FLUID MANAGEMENT	• Assess for hypovolaemia and correct as required. • Avoid excessive resuscitation or 'maintenance' fluids • Anticipate and monitor ongoing fluid losses	

VTE PROPHYLAXIS	• ***All patients enrolled in ASCOT-ADAPT or REMAP-CAP (anticoagulation domains)***	• ***As per trial protocol***
	Hospitalised adults with: • mild COVID-19 • <u>OR</u> severe and critical COVID-19 <u>AND</u> no contra-indication to anticoagulation e.g. risk for major bleeding	Enoxaparin 40mg SC once daily (standard prophylaxis) • Adjust dose for impaired renal function (NB Therapeutic-dose anticoagulation is not beneficial and probably hazardous when initiated prophylactically in severe and critical COVID-19)
	Hospitalised adults with **moderate** COVID-19 <u>AND</u> no contra-indication to anticoagulation e.g. risk for major bleeding (NB moderate = *stable adult patient presenting with shortness of breath and/or reduction in resting oxygen saturation while breathing air. Able to maintain oxygen saturation ≥92% (or ≥90% for patients with chronic lung disease) with up to 4 L/min oxygen via nasal prongs*)	Therapeutic dose anticoagulation **should be considered** over standard prophylaxis for up to 14 days, or until clinical recovery (discharge or resolved hypoxia) Enoxaparin 1mg/kg SC twice daily (max 150mg BD) • Adjust dose for impaired renal function **All other patients should receive standard prophylaxis** as detailed above
	Hospitalised pregnant adults with mild OR severe/critical COVID-19 UNLESS: • Delivery expected within 24 hours (if only on enoxaparin 40mg SC once daily then 12 hourly) • Platelets < 50 • Actively bleeding / coagulopathy • Severe hypertension (>160/110)	Enoxaparin 40mg SC once daily (standard prophylaxis) • dose adjustment may be necessary if current weight ≥90kg
	Hospitalised pregnant or postpartum adults with moderate COVID-19 AND no contra-indication to anticoagulation (as above)	Consider therapeutic anticoagulation as for non-pregnant adults (above)
	Anticoagulation in pregnancy should be considered for a longer duration if post-partum or has additional risk factors for VTE (discuss with Obstetrics)	
INTENSIVE CARE	Regular, open and early discussions between ward-based clinicians and local ICU team is strongly encouraged. In addition to local referral guidelines, ICU review should be prompted by the following: • Significant oxygen requirement (e.g. requiring FiO2 of >40% to maintain SpO_2 >92%, or needing CPAP) • Increased work of breathing with impending respiratory failure • Haemodynamically unstable and / or hypotension not responsive to fluid bolus • Rapidly worsening tachypnoea or hypoxaemia Detailed clinical guidance for ICU care of COVID-19 is beyond the scope of this guideline	
ANTIBIOTIC THERAPY	Antibiotics should not be used to treat COVID-19 pneumonitis: bacterial co-infection is uncommon.	
	Severe/critical COVID-19 especially with any deterioration occurring >7 days post onset and/or >3 days after hospital admission	• Evaluate for secondary infection, including hospital-acquired infection • Discuss with local Infectious Diseases / Microbiology team if concern for secondary infection

COMMUNICATION & HOLISTIC CARE	Encourage for all patients: • Clearly communicate typical symptoms and anticipated clinical course with patient, family/whānau or carers • Reinforce importance of complying with all Public Health messages, including self-isolation and testing • When possible, explain risks, benefits and likely outcomes of treatments with patients, family/whānau or carers • Use an interpreting service to assist communication if required • Facilitate regular clinical updates, and video calls between patient family/whānau or carers • Routinely refer to local cultural and/or spiritual support services • Consider early involvement of Palliative Care and/ or Liaison Psychiatry services to assist with symptom management, particularly anxiety, dyspnoea and delirium/agitation • Ensure appropriate housing, financial and social support is in place prior to discharge (including a working phone). If concerns, refer to social work • If welfare or cultural support issues identified, liaise with Public Health or Regional Isolation Quarantine (RIQ) according to regional processes as part of **discharge planning**	
	• Ensure Maternity services including lead maternity carer are alerted so wrap-around antenatal and post-natal care can be provided for the mother and baby	
THERAPIES FOR EXISTING INDICATIONS	• Nocturnal CPAP for Obstructive Sleep Apnoea (inpatients)	Consider changing usual vented CPAP mask to a non-vented mask + expiratory port + filter (decision depends on equipment availability and staff expertise)
	• ACE-inhibitors / ARBs • Oral contraceptive pill (with or without oestrogen)	• Usual care (i.e. may be continued in COVID-19 unless otherwise contra-indicated)
	• Corticosteroids for asthma/COPD (inhaled or oral, with or without bronchodilators)	• Usual care • Do not use a nebuliser unless definite clinical need
	• Oral menopausal hormone therapy / HRT	• Consider stopping until after recovery
	• All pregnancy-related supplements and medications should be continued	
SURGERY	• Elective minor surgery should generally be deferred until at least four weeks, and major surgery until 8-12 weeks, following recovery from COVID-19 if patient outcome is not compromised • Acute surgical procedures that are indicated during active COVID-19 infection should be discussed with local ID and infection control services • Comprehensive preoperative and ongoing assessment must be carried out to ensure optimal clinical decision-making	
	• Caesarean section (including emergency) should not be deferred if clinically indicated, e.g. if needed for maternal resuscitation or immediate fetal concern; mode of delivery should otherwise remain based on obstetric indication	

COVID-19 Therapeutics: patients **not requiring oxygen**

There are increasing therapeutic options for COVID-19 in patients who do not require oxygen. The main benefit of these treatments is in reducing rates of hospitalisation, with a possible small reduction in mortality. These treatments have not been studied in vaccinated individuals or in people infected with the Omicron variant, both of which are anticipated to significantly reduce the benefit of treatment compared with unvaccinated validation cohorts. Given limitations in available stock, it is therefore of critical importance that treatments are prioritised to patients with the highest absolute risk of developing severe COVID-19. Based on currently available data and international guidelines, we suggest prioritisation of treatment using the following risk categories, listed in descending order:

1.	Immunocompromised and not expected to mount a response to vaccination (regardless of vaccination status) particularly if older age or additional **risk factors for severe disease**. OR unvaccinated and over 65 years of age
2.	Unvaccinated and over 50 years of age OR unvaccinated and any age with multiple **risk factors for severe disease**.
3.	Vaccinated and over 65 years of age OR vaccinated and over 50 years of age and multiple **risk factors for severe disease**
4.	Vaccinated and any age with multiple **risk factors for severe disease**
5.	All other individuals

Notes:

- Māori or Pacific ethnicity should increase risk group by one category.
- 'Vaccinated is considered to be completion of primary course > 7 days ago
- This suggested prioritisation may differ from PHARMAC access criteria for individual treatments

MODALITY	PATIENT SUB-GROUPS	RECOMMENDATION
STEROIDS	Adults who do not require oxygen AND are in **risk categories 1, 2 or 3** AND are within 10 days of symptom onset AND are ineligible for other COVID-19 therapeutics	Consider inhaled budesonide 800micrograms BD for up to 14 days if respiratory symptoms Do not use systemic steroids to treat COVID-19
	Adults without oxygen requirement, but another evidence-based indication for systemic steroids (e.g. asthma/COPD exacerbations)	Steroids as per usual practise

ANTIVIRALS	***Currently remdesivir is the only antiviral available in NZ and supply is limited. Prescribers should prioritise patients at highest risk of severe disease.*** ***Do not admit patients to hospital specifically for remdesivir treatment.***	
	Adults with COVID-19 who do not require oxygen AND are within 7 days of symptomatic illness AND fulfil any of: • Immunocompromised and not expected to mount an adequate response to COVID-19 vaccination • Unvaccinated with 3 or more risk factors* • Vaccinated with 5 or more risk factors* **Risk factors include age 65 or older, Māori or Pacific ethnicity, and other comorbidities associated with increased **risk of severe COVID-19***	Consider remdesivir: • 200mg IV on day 1, then 100mg IV q24h for further 2 days (maximum 3 days total)
	Adults with COVID-19 after day 7 of illness	• Do not start remdesivir • Complete course (3 days) if started earlier in illness
	Adults with severe immunocompromise with any stage/severity of COVID-19	Discuss with local infectious diseases team
	Pregnancy (meeting the same clinical criteria as above)	• Use remdesivir if >12/40 gestation as per Adult Guideline indications with the same dosing as above • Remdesivir is compatible with breastfeeding
ANTIBODY THERAPY	Adults with **any severity of illness**	**Do not use casivirimab/imdevimab (Ronapreve)** due to lack of efficacy against Omicron, and negligible Delta variant transmission in New Zealand currently *Guidance about use in specific cases if advised by an expert clinician is available **here**.

COVID-19 Therapeutics: patients **requiring oxygen**

MODALITY	PATIENT SUB-GROUPS	RECOMMENDATION
STEROIDS	Adults with sustained oxygen requirement	Dexamethasone 6mg* daily PO/IV for up to 10 days OR until hospital discharge Consider a minimum dexamethasone duration of 5 days, if discharged within this time *consider dexamethasone 12mg PO/IV once if would qualify for **immunomodulation**, but medication is unavailable within next 24 hours

	Pregnancy with sustained oxygen requirement to maintain SpO2 ≥94%	If steroids needed for fetal lung maturation (usually < 34^{+6} weeks): • dexamethasone 6mg IM every 12 hours for four doses • THEN either prednisone 40mg PO daily, OR hydrocortisone 80mg IV twice daily If steroids <u>not</u> required for fetal lung maturation, use non-fluorinated steroids: • prednisone 40mg PO daily OR hydrocortisone 80mg IV twice daily OR methylprednisolone 40mg IV once daily Total duration is 10 days total OR until discha ge, whichever is sooner.
	Risk of **gestational diabetes:** monitor blood glucose levels closely and start treatment if elevated.	
ANTIVIRAL THERAPY	***All patients enrolled in ASCOT-ADAPT trial (anti-viral domain)***	***As per trial protocol & randomisation (in addition to remdesivir, if indicated below)***
	Adults with new sustained oxygen requirement within first 7 days of illness	• Do not start remdesivir • Complete course (3 days) if started earlier in illness
	Adults with COVID-19 after day 7 of illness	• Do not start remdesivir • Complete course (3 days) if started earlier in illness
	Adults with severe immunocompromise with any stage/severity of COVID-19	Discuss with local infectious diseases team
	Pregnancy (meeting the same clinical criteria as above)	• Use remdesivir if >12/40 gestation as per Adult Guideline indications with the same dosing as above • Remdesivir is compatible with breastfeeding
ANTIBODY THERAPY	Adults with **any severity of illness**	**Do not use casivirimab/imdevimab (Ronapreve)** due to lack of efficacy against Omicron, and negligible Delta variant transmission in New Zealand currently *Guidance about use in specific cases if advised by an expert clinician is available **here**.
	In patients receiving systemic steroids in combination with immune modulation, we recommend screening for, and consider empiric treatment of latent infection, e.g. Hepatitis B or strongyloidiasis (in patients who have lived in an endemic region)	
	There are no trials of immune modulation therapies currently recruiting in New Zealand	

IMMUNE MODULATION THERAPY	Adults with moderate COVID-19 • AND receiving systemic steroids • AND elevated CRP or other evidence of severe systemic inflammation OR clinically deteriorating • AND there is not another active, severe concurrent infection	Give tocilizumab: • 8mg/kg IV (actual body weight) rounded to nearest 200mg (max dose 800mg), as a single dose • *Notes: risk of secondary infection may be increased; CRP response is inhibited, and consequent reduction in CRP does not necessarily correlate with response to treatment* OR baricitinib: • 4mg PO/NG daily for 14 days or until hospital discharge • Reduce to 2mg PO daily if eGFR 30-60mL/min • Reduce to 1mg PO daily if eGFR 15-29mL/min* • Do not use if eGFR <15mL/min • Avoid in pregnancy or breastfeeding • Baricitinib is a **section 29** product *2mg PO every 48 hours is an acceptable alternative
	Adults with severe / critical COVID-19 requiring non-invasive or mechanical ventilation or organ support: • AND receiving systemic steroids • AND there is not another active, severe secondary infection	Give tocilizumab as above • Start as soon as possible if requiring NIV, mechanical ventilation or other organ support Baricitinib may be considered as an alternative to tocilizumab if unavailable (as above) If bar citinib commenced earlier in illness: • Continue the planned course as above • Do not add tocilizumab • If enteral route compromised, discuss potential switch with Infectious Diseases as soon as possible
	COVID-19 not meeting the criteria above	Do not use immune modulation therapy
	Pregnancy (meeting the same clinical criteria as above)	Give tocilizumab (same dosing as above): • *Notes: Tocilizumab crosses the placenta after 28/40, but no evidence of harm to date. Suggest deferring live vaccination (i.e. Rotarix, BCG) up to 6 months in neonates with antenatal exposure. All other vaccinations are safe.* • *Compatible with breastfeeding.* • *May cause raised ALT and thrombocytopenia, mimicking pre-eclampsia / HELLP.* • *Do not use baricitinib (as above)*

Discharge Planning and Follow-up

Patients with Suspected, Probable or Confirmed COVID-19 who are being considered for discharge need to have specific decisions made about the following aspects of post-discharge care:

FURTHER INVESTIGATIONS	• Follow-up investigations are not universally required after COVID-19 • A repeat chest x-ray in 6-12 weeks to confirm resolution of pulmonary opacities should be arranged for individuals with significant radiographic abnormalities and / or risk factors for lung cancer • Ensure follow up serology is arranged for 'probable' cases

DISCHARGE DESTINATION	• Anyone with COVID symptoms or suspected infection being discharged before PCR results are available should be tested using a RAT. If the RAT (or a PCR) is negative, the person should be advised to stay home until symptoms resolve and seek a further test if symptoms worsen. • Anyone who tests positive (on RAT or PCR) should be able to be discharged home but should be linked in through the Care in the Community Model if needed for follow-up, and household members should be advised to self-isolate as per standard advice for positive cases. Note that positive RAT results need to be recorded in My Covid Record. • The local Medical Officer of Health does not need to be notified of discharge of a positive case.	
CLEARANCE FROM ISOLATION	• The decision to end isolation should be consistent with Public Health policies • Release from isolation is based on determination that the person is no longer infectious: this is now taken as **10 days from date of onset of symptoms or date of positive test** (whichever is earlier, starting from day zero). The exception is for someone who is immunocompromised, where RAT testing is useful (eg. two tests 24 hours apart if negative would provide reasonable assurance). However, it is advisable to seek the advice of an infectious disease specialist or microbiologist for immunocompromised cases.	
	All patients	• **Encourage vaccination if not completed eligible vaccination course (including booster).** Vaccination is recommended from 4 weeks after clinical recovery, even if treated with anti-SARS-CoV-2 antibody therapy (convalescent plasma or monoclonal antibody such as Ronapreve) • Educate about anticipated gradual recovery from COVID-19, and potential for persistent symptoms. Encourage those with persistent symptoms after 6 weeks to arrange assessment by their GP.
	Patients with significant respiratory failure (and/or persistent dyspnoea), or other persistent organ dysfunction	Specialist clinic follow-up, investigations and support following discharge (as advised by local specialty services)
	Patients discharged with nocturnal CPAP (usual OR new device)	Consider providing a non-vented mask + expiratory port + filter if discharging to MIQ (depending on equipment availability and staff expertise). Sleep service remote follow-up within 48 hours of hospital discharge is recommended if non-vented mask set up is used. Can transition to vented mask on return to own home.
	Pregnancy (or recently post-partum)	• VTE prophylaxis - refer to specific guidelines above • Recommend follow up growth scan within 2 weeks • If possible, delay follow-up CXR until post-partum

Links to other guidelines

- **Australian COVID-19 living guidelines:** https://covid19evidence.net.au/
- **NICE (UK) living guideline:** https://www.nice.org.uk/guidance/ng191
- **National Institute of Health (USA):** https://www.covid19treatmentguidelines.nih.gov/
- **WHO COVID-19 living guideline: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1**
- **Ontario COVID-19 Science Advisory Group guideline (Canada) : https://covid19-sciencetable.ca/sciencebrief/clinical-practice-guideline-summary-recommended-drugs-and-biologics-in-adult-patients-with-covid-19-version-9-0/**
- **Australian guidance for Pregnancy and perinatal care:** https://covid19evidence.net.au/

Therapeutics Technical Advisory Group | Te Rōpū Haumanu Kowheori-19

Date: 23 March 2022

The Therapeutics Technical Advisory Group (Therapeutics TAG) was established by the Ministry of Health in August 2021 to provide expert advice on existing and emerging medicines for use in the management of COVID-19.

Guidance for temporary prioritisation of remdesivir for early COVID-19 in people not requiring oxygen

The intention of this document is to provide temporary guidance for the prioritisation of remdesivir to patients with COVID-19 likely to be at the very highest risk of progression to requiring in-hospital treatment. It is anticipated that this guidance will change with increased availability of COVID-19 community therapeutics in the coming months.

PHARMAC succesfully negotiated delivery of 5000 intravenous doses of remdesivir to New Zealand in late February 2022. Temporary access criteria for remdesivir were published on the 4th of March 2022. These criteria differ from access criteria released on 28th of February 2022, and are likely to be revised again following a consultation process on proposed access criteria for oral COVID-19 antiviral agents.

The 5000 doses of remdesivir obtained are sufficient to treat approximately 1000 people. However, the New Zealand COVID-19 'surge' in transmission associated with the Omicron variant has resulted in vast numbers of people being infected in a short period of time, which has created a significant mismatch between the availability of remdesivir courses and the infected eligible population.

The Therapeutics Technical Advisory Group (TAG) considers that it is reasonable to offer remdesivir to people with early COVID-19 in the community who are at very high risk of progression to requiring in-hospital treatment. However, we acknowledge there is limited evidence to inform the efficacy of remdesivir in the current phase of the COVID-19 pandemic and that the significant resource constraints faced by most of the New Zealand health system presently will limit the capacity to deliver intravenous remdesivir to outpatients.

The Therapeutic TAG have already provided guidance on the use of remdesivir in patients hospitalised with COVID-19. That guidance can be found in the latest version of the guideline: Clinical management of COVID-19 in hospitalised adults, which is updated regularly.

Therapeutic Technical Advisory Group temporary recommendations

Although the temporary PHARMAC access criteria describe a broader eligible population, the COVID-19 Therapeutics TAG recommend prioritisation of remdesivir (if available) to people who fulfil all of the following:

1. Are within 7 days of symptom onset of confirmed (or probable*) COVID-19 illness
2. AND have not developed a sustained requirement for supplemental oxygen since symptom onset
3. AND have persistent symptoms, with no evidence of clear clinical improvement
4. AND either:
    a. Have **not completed an effective course of vaccination*** AND:
        i. Are over 60 years old if Māori or Pasifika OR over 70 years old if other ethnicity
        ii. AND have at least two other risk factors for severe COVID-19
            - *Other risk factors include chronic kidney disease, significant cardiac disease, chronic lung disease, active cancer, obesity, uncontrolled hypertension, uncontrolled diabetes, chronic liver disease, or immunocompromise.*

    b. OR are **severely immunocompromised**[&], regardless of vaccine status that are not anticipated to mount an adequate immune response to SARS-CoV-2 infection

Additional recommendations:

- Within the above groups, Māori or Pasifika, and those with higher clinical risk (e.g. older age, more risk factors) should be prioritised above other otherwise similarly eligible patients.
- We acknowledge that some younger, very multimorbid individuals, or those with uncommon, very high risk conditions (e.g. Down syndrome) may have a similar risk of COVID-19 associated hospitalisation to the suggested priority groups above, and could be considered for remdesivir treatment on a case by case basis after discussion with a local expert COVID-19 clinician (e.g. Infectious Diseases).
- We recommend that remdesivir treatment **should not exceed three doses**, consistent with the treatment protocol used in the PINETREE trial.[1]
- We recommend against hospital admission for the sole reason of facilitating remdesivir treatment.

* **Incomplete vaccination course** is considered by the COVID-19 Therapeutics TAG to be:

- Fewer than 2 doses of a SARS-CoV-2 vaccination course in the seven days prior to infection
- OR recipients of a 2 dose vaccination course, with the most recent dose more than 6 months ago

[&] **Severe immunocompromise** unlikely to mount an adequate immune response to SARS-CoV-2 vaccination or infection is considered to include the following clinical scenarios:

- Solid organ transplant recipient, particularly if within 12 months of transplantation, if requiring more than routine maintenance immunosuppression, treated with mycophenolate mofetil, or treated for rejection within past 12 months
- Within 24 months of haematopoietic stem cell transplant or CAR-T cell therapy.
- Graft-versus-host disease treated with multi-modal immunosuppressive therapy

- Treated B-cell haematologic malignancy (e.g. multiple myeloma, chronic lymphocytic leukaemia, lymphoma) within the past 6 months
- Receipt of anti-CD20 monoclonal antibody therapy (e.g. rituximab) within the past 12 months
- Primary or acquired hypogammaglobulinaemia (IgG <3), even if now on replacement immunoglobulin
- Primary immunodeficiency associated with severe B-cell or combined cellular defects
- Advanced HIV with CD4 <200
- Other conditions (on case by case basis) felt to have profound immunocompromise on the basis of combined immunosuppression, functionally equivalent to the above groups.

Context and basis for recommendations

Remdesivir is currently (March 2022) the only antiviral agent with efficacy against SARS-CoV-2 available in New Zealand. Additionally, remdesivir is currently only available as an intravenous formulation.

Remdesivir has been evaluated as a treatment for COVID-19 in hospitalised patients in several large-scale, multicentre, randomised controlled trials. While a trend to benefit in secondary outcomes was suggested in some trials (e.g. small improvement in time to clinical recovery) there was no reduction in COVID-19 associated mortality.[2-4]

Treatment of 'high risk' patients with remdesivir early in COVID-19 illness was evaluated by the Gilead-sponsored PINETREE study.[1] In this trial, 562 unvaccinated outpatients in the first 7 days of symptomatic COVID-19 illness were randomised to either a three-day course of intravenous remdesivir or placebo. The definition of 'high risk' included age over 60 OR any single risk factor for severe disease (e.g. hypertension). These patients were recruited from September 2020 to April 2021, which preceded widespread circulation of the Delta or Omicron variants of concern. The primary outcome was 'COVID-19 associated hospitalisation or death'. Patients treated with remdesivir had a hospitalisation rate of 0.7%, compared with 5.3% in the placebo group (HR 0.13, 95% CI 0.03 to 0.59, p=0.008). There were no deaths in either group. The number of patients needing treatment (NNT) to prevent one hospitalisation was 22. The strength of evidence for remdesivir in early illness has been assessed as 'moderate' (grade BIIa) by the US NIH and UK NICE COVID-19 treatment guideline panels (NICE COVID-19 guidance; NIH COVID-19 Treatment Guidelines).

While there have been no subsequent trials evaluating contemporary outpatient use of remdesivir, the results of the PINETREE study broadly align with other trials of antiviral therapy for early treatment of 'high risk' outpatients (molnupiravir and nirmatrelvir/ritonavir respectively).[5,6]

However, there are important limitations on the applicability of these trials. There are no data to inform the benefit of outpatient antiviral treatment for: a) vaccinated people, or people with previous COVID-19 b) people infected with the Omicron variant of concern or c) children and young people (only 8 patients between age 12-18 years of age in PINETREE).[1] Additionally, there were too few immunocompromised patients or patients with active cancer included in these trials to allow for robust estimation of efficacy in these important subgroups (10% in PINE TREE, <1% in EPIC-HR, 2% in MOVe-OUT).[1,5,6]

The contemporary NNT for early remdesivir treatment to prevent one hospitalisation is estimated to be significantly higher than the 22 observed in the PINETREE trial. Firstly, the rate of COVID-19 hospitalisation associated with the Omicron variant is only 40-50% of that observed with the Delta variant.[7,8] Secondly, in spite of the immune-evasiveness of the Omicron variant, three vaccine doses continues to afford significant protection against COVID-19 hospitalisation (over 70% in the UK)[8] and mechanical ventilation or death (94% in the USA).[9] However, the protective effect of three doses of mRNA vaccine against Omicron-associated hospitalisation is reduced in older adults with multiple comorbidities and may be reduced in immuncompromised people.[10-12]

In summary, there is moderate evidence from a single study to suggest that treatment with a 3 day course of intravenous remdesivir reduces risk of hospitalisation in unvaccinated 'high risk' adults. The relative benefit of remdesivir treatment is likely to be at least halved by infection with the Omicron variant, and may be reduced to insignificance in most people who have completed vaccination with a booster. Some groups of patients with a very high absolute risk of hospitalisation may be more likely to benefit from remdesivir treatment than others, but there are no published data to support this hypothesis.

In New Zealand, the critical consideration for use of remdesivir is its extremely limited availability, which is currently sufficient to treat fewer than 1000 patients. This supply is mismatched against the vast numbers of people with active COVID-19 in the community (120,000 on March 18th). As a result, it is predicted that there will be insufficient courses of remdesivir to treat the eligible population described by the revised PHARMAC temporary access criteria for remdesivir, and further prioritisation will be required. A second significant consideration is the large healthcare resource required to deliver a three-day course of intravenous remdesivir to people in the community. Furthermore, these healthcare worker, healthcare facility and healthcare system resources are all currently under unprecedented strain due to the surge of Omicron-variant COVID-19 cases. Lastly, due to the over-representation of Māori and Pasifika among people hospitalised with COVID-19, it is critical that additional healthcare resource is deployed to overcome this inequity.

After considering the relevant literature and the practical challenges facing the New Zealand healthcare system during the Omicron 'surge' in community cases, the Therapeutics TAG considers that it is reasonable to offer remdesivir to people with early COVID-19 who are at very high risk of requiring hospital treatment, as outlined in the recommendations above. However, given limitations in the evidence, and the significant resource constraints highlighted, we consider community remdesivir treatment to be an optional component of COVID-19 care, which may be considered where it is practicable.

These recommendations are temporary, and may be revised following increased availability of remdesivir, arrival of other therapeutic agents for treatment of early COVID-19 (such as nirmatrelvir/ritonavir and molnupiravir) or both.

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COVID-19

Clinical Management of COVID-19 in Hospitalised Adults (including in pregnancy)

Introduction

Updated 1 April 2022 – Next planned update 6 May 2022

- **NEW** figure added giving overview of COVID-19 management **(page 2)**
- Revision of advice for treatment of patients not requiring oxygen to include recommendation for use of Paxlovid (nirmatrelvir + ritonavir) and amended advice for use of remdesivir and budesonide.
- Advice that the Ministry of Health Āwhina app provides notifications when guideline updates are made.
- Additional recommendation advocating for specialist input for management of COVID-19 in **severely immunocompromised** individuals
- New recommendation to consider individual balance of risks and benefits when prescribing **remdesivir** to people with eGFR <30ml/min. Addition of optional two-dose prescription in this group.
- New recommendation **against routinely continuing dexamethasone** after hospital discharge if completed 5 days treatment
- Amended order of **immunomodulation treatment** options for patients with 'moderate' COVID-19
- Updated dosing recommendation for **tocilizumab** to avoid potential wastage of drug (round to nearest whole available vial)
- Approval of **switch from baricitinib to tocilizumab** for patients who deteriorate to require non-invasive or mechanical ventilation
- Updated **'clearance from isolation'** section to reflect different isolation recommendations between hospitalised and community patients
- Amended recommendation for **timing of vaccination** after recovery from COVID-19

New content in this update is highlighted in red.

This guideline is intended to be an accessible summary of hospital management of **ADULTS** (including in pregnancy**)** with **confirmed or probable COVID-19**. It has been adapted from international 'living' guidelines for the New Zealand context by an advisory group of New Zealand clinicians, including representation from Infectious Diseases, Respiratory Medicine, Intensive Care, General Medicine, Obstetric Medicine, Primary Care, Emergency Medicine and Pharmacy.

New evidence informing the optimal management of patients with COVID-19 continues to accumulate rapidly. This document will be reviewed and updated periodically, or in response to significant changes in evidence and/or recommendations by international guideline groups. Download the Ministry of Health **Āwhina app** to be notified when guideline updates are made.

Further detailed guidance, including treatments that are either not recommended, or recommended only within a clinical trial, can be accessed in links to international guidance at the end of this document. Local specialist services with expertise in managing COVID-19 may consider emerging treatments outside of this guideline.

Additional details or differences on managing a pregnant woman are highlighted in orange rows just below the adult guidance.

Lastly, the management of COVID-19 in **severely immunocompromised patients** presents unique challenges that are outside the scope of this guideline. Specialist advice from a patient's primary specialist ***and*** an Infectious Diseases physician is strongly recommended.

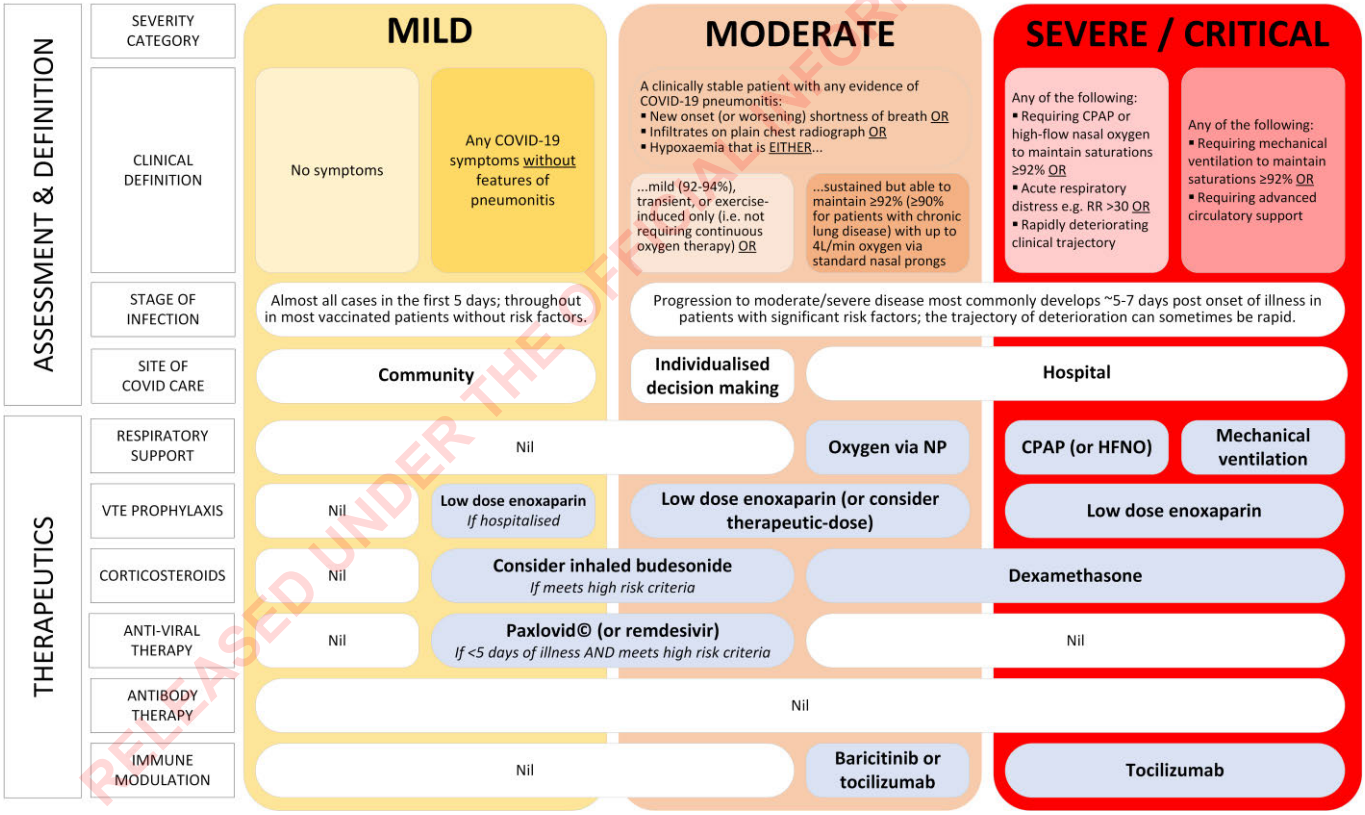

Figure 1 - Severity assessment and therapeutic options in COVID-19 management.

Initial Management

	MILD	MODERATE	SEVERE / CRITICAL
DEFINITION	No symptoms **OR** URTI symptoms only **OR** cough, new myalgia or asthenia <u>without</u> new shortness of breath or reduction in resting oxygen saturation	Stable adult patient presenting with shortness of breath and/or reduction in resting oxygen saturation while breathing air. Able to maintain oxygen saturation ≥92% (or ≥90% for patients with chronic lung disease) with up to 4 L/min oxygen via nasal prongs	Adult patients meeting any of the following criteria: • Respiratory rate ≥30/min • Oxygen saturation <92% on 4L/min oxygen via nasal prongs • Clinically deteriorating
	Pregnancy: use an oxygen saturation **target of ≥ 94%** rather than ≥92%		
BASELINE TESTING & WORK-UP	• Pulse oximetry • Other tests only as clinically indicated • Low value testing is discouraged	• FBC, Creat, electrolytes, LFTs, CRP • ECG only if specific indication • Chest x-ray • Venous blood gas (conside arterial) • Investigations for CAP (e.g. urinary antigens sputum PCR panel) if radiography suggests **bacterial infection** • Consider **d-dimer & ferritin**	• FBC, Creat, electrolytes, LFTs, CRP • ECG • Chest x-ray • Venous blood gas (consider arterial) • Investigations for CAP (e.g. urinary antigens, sputum PCR panel) if radiography suggests **bacterial infection** • Blood cultures if febrile or shocked • Coag screen, d-dimer, ferritin, BNP, Troponin
	• Note – in vaccinated individuals with Omicron variant infection, COVID-19 may not be the primary diagnosis responsible for hospital presentation. It is important to consider concurrent non-COVID-19 medical conditions during evaluation.		
	• **Pregnancy:** also request urine protein:creatinine ratio, coagulation profile, group and screen (or cross match if delivery is thought to be imminent) • *NB* CXR and CT chest / CTPA can safely be performed in pregnancy if clinically indicated. • Laboratory results should be cautiously interpreted, using pregnancy-specific ranges where available. There are no validated pregnancy-specific values for D-dimer; consider monitoring trend for prognostic purposes in severe/deteriorating COVID-19.		
TREATMENT ESCALATION PLANNING	• Assess ability to safely isolate in community. • Notify and refer through local pathways • Consider & document **risk factors for severe COVID-19**	• Assess & document individual **risk factors for poor outcome** • Early discussion of patient goals of care, including existing advanced care plans, with patient and their family/whānau • Early, clear documentation of resuscitation decision and treatment escalation plan for <u>all</u> patients, specifically including appropriate modalities of respiratory support	
	• **NOTE – any new deterioration > 5 days post onset of illness requires careful assessment, observation & judgement. Severe COVID-19 frequently develops with a rapid deterioration**		
	• For pregnant and post-partum observations, utilise a maternity-specific chart (if available) • Recommend early consultation with Obstetrics, Anaesthesia and NICU (and Obstetric Physician if available)		
DISPOSITION DECISION	• Encourage **discharge** • Liaise with local Public Health Unit or Regional Isolation and Quarantine (RIQ) according to regional processes	• Discuss with local COVID team • Admit to hospital if **Sa02 <93%** • Consider discharge if Sa02 ≥93% according to local protocols and availability of	• Admit to hospital • ICU and/or Respiratory review

		acute community COVID-19 care (e.g. primary care or hospital in the home service)	
MONITORING & MARKERS OF CLINICAL DETERIORATION	• Risk of deterioration is significantly reduced by vaccination and infection with Omicron variant. Individualised risk assessment should include consideration of vaccination status, day of illness, age, immunocompromise and comorbidities that **increase risk of severe disease**. • Ferritin and d-dimer are suggested as severity/prognosis markers, as part of an overall assessment • Monitor for progressive respiratory failure and sepsis, especially after day 5 of illness • Only repeat CXR during admission for confirmed COVID-19 for specific clinical indications • Perform a chest CT scan only if it would change management, in particular if concern for pulmonary embolism • Anticipate complications such as delirium, pulmonary embolism, other thromboembolism, arrhythmias, cardiac impairment, acute kidney injury, sepsis, shock and multi-organ dysfunction, and address using existing standards of care. Also be aware of potential medication complications • Repeat **baseline investigations** periodically in patients who are not clearly improving, in order to detect & manage the above complications		
	Additional considerations in pregnancy: • Screen for pre-eclampsia in all pregnancies > 20/40 gestation and review at each assessment: i.e., systolic BP ≥ 140mmHg and/or diastolic ≥ 90, worsening peripheral oedema, headache, visual changes or upper abdominal pain. Risk of pre-eclampsia is increased in COVID-19. • Consider repeating laboratory investigations if there is a change in maternal condition • Appropriateness and frequency of fetal heart rate monitoring and ultrasound to be considered on an individual basis, accounting for gestational age and clinical severity. Consider parameters for delivery (in discussion with neonatologists, anaesthetists ± intensive care team) • Consider steroids for the fetal lung maturation, and magnesium sulphate for neuroprotection or severe pre-eclampsia as per local obstetric guidelines • Consider emergency delivery if required for maternal resuscitation (including need for prone positioning) or for immediate fetal concern		
NOTIFICATION	• Discuss all cases with local COVID team at the earliest opportunity, according to local protocols • If not already notified according to regional process, (e.g. by laboratory) contact local Public Health Unit		
	• If hospitalised, all pregnant women should have multidisciplinary assessment by obstetricians, midwives, neonatologists +/- an obstetric physician at the earliest opportunity • Recommend notification of all antenatal and postnatal cases to New Zealand Registry of COVID-19 in Pregnancy		
CLINICAL TRIALS	• As the optimal management of COVID-19 is not yet known, the **standard of care is to be offered enrolment in a clinical trial,** if available • **All** patients should be screened for eligibility for a locally available COVID-19 clinical trial (e.g. 'REMAP-CAP' and 'ASCOT-ADAPT')		

COVID-19 Therapeutics: patients **not requiring oxygen**

There are increasing therapeutic options for COVID-19 in patients who do not require oxygen. The main benefit of these treatments is in reducing rates of hospitalisation, with a possible small reduction in mortality. These treatments have not been studied in vaccinated individuals or in people infected with the Omicron variant, both of which are anticipated to significantly reduce the benefit of treatment compared with unvaccinated study cohorts. When stocks are limited, it is therefore of critical importance that treatments are prioritised to patients with the highest absolute risk of developing severe COVID-19. The recently released access criteria for nirmatrelvir/ritonavir (Paxlovid) outline groups who are felt to be at high absolute risk of hospitalisation in New Zealand. As such, **we recommend that all treatments** (including remdesivir and budesonide) **for patients not requiring oxygen be prioritised to those meeting 'high risk' criteria**:

1) At least ***five* of the following:**
    a. Any combination of the **risk factors for severe COVID-19 disease**[1] (with each individual condition counting as one risk factor)
    b. Māori or any Pacific ethnicity
    c. Patient is aged 65 years and over OR is 50 years and over and has not completed a full course of vaccination[2]
2) OR is **severely immunocompromised**[3] and not expected to reliably mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection, regardless of vaccination status

For these treatments, patients should not already have COVID-19 associated pneumonitis requiring oxygen. If a patient requires oxygen for COVID-19, **different therapeutics recommendations** apply.

Notes:

[1] **Risk factors** are detailed on the Ministry of Health (MOH) website and include: obesity, chronic lung disease, chronic kidney disease, heart disease, diabetes, hypertension, chronic liver disease, active malignancy, chronic neurologic disease and severe mental health illness.

[2] **Incomplete vaccination** is defined as fewer than two doses by the linked **Ministry of Health document.** However, for the purposes of this guideline, we currently consider incomplete vaccination to be:

- Fewer than 2 doses of vaccine
- OR 2 doses of vaccine, with second dose < 7days or > 6months before symptom onset

[3] The definition of **immunocompromise** in PHARMAC access criteria aligns with the eligible population for a **three-dose primary vaccine** series. However, a subgroup of **severely immunocompromised** individuals are at higher risk of severe outcomes, including:

- Solid organ transplant recipient, particularly if within 12 months of transplantation, if requiring more than routine maintenance immunosuppression, treated with mycophenolate mofetil, or treated for rejection within past 12 months
- Within 24 months of haematopoietic stem cell transplant or CAR-T cell therapy.
- Graft-versus-host disease treated with multi-modal immunosuppressive therapy
- Treated B-cell haematologic malignancy (e.g. multiple myeloma, chronic lymphocytic leukaemia, lymphoma) within the past 6 months
- Receipt of anti-CD20 monoclonal antibody therapy (e.g. rituximab) within the past 12 months
- Primary or acquired hypogammaglobulinaemia (IgG <3), even if now on replacement immunoglobulin
- Primary immunodeficiency associated with severe B-cell or combined cellular defects
- Advanced HIV with CD4 <200
- Other conditions (on case by case basis) felt to have profound immunocompromise on the basis of combined immunosuppression, functionally equivalent to the above groups

MODALITY	PATIENT SUB-GROUPS	RECOMMENDATION
ANTIVIRALS	Adults who meet **high risk criteria** AND are within 5 days of symptom onset AND do not have severe hepatic (Childs-Pugh class C) *or* renal impairment (eGFR <30ml/min) AND do not have a potentially serious **drug-drug interaction** with ritonavir	Give Paxlovid (nirmatrelvir and ritonavir):* • (nirmatrelvir 300mg + ritonavir 100mg) PO q12h for 5 days • eGFR 30-59ml/min: nirmatrelvir 150mg + ritonavir 100mg po q12h for 5 days • Use barrier contraception for 7 days after last dose **NB Paxlovid **prescriber advice available here.** Management of **common drug interactions highlighted here**. Stock is likely to be available for hospital use later than community pharmacies*
	Adults who meet **high risk criteria** AND are unable to receive Paxlovid AND are within 7 days of symptom onset *Guidance for further prioritisation of remdesivir to patients at highest risk is available **here**.*	Consider remdesivir: • 200mg IV on day 1, then 100mg IV q24h for further 2 days (maximum 3 days total) • Limited data of safety in patients with eGFR <30ml/min or peritoneal dialysis.* Use if benefits felt to clearly outweigh potential risks. Likely to be safe in haemodialysis. **Consider a two dose regimen (i.e. omission of day 3 dose) for patients with eGFR<30: modelling suggests this may provide equivalent drug concentrations to patients with normal renal function.*
	Adults with COVID-19 after day 7 of illness *Recommend discuss **severely immunocompromised** patients with Infectious Diseases*	• Do not start remdesivir • Complete course (3 days) if started earlier in illness
	Pregnancy (meeting the same clinical criteria as above)	• Do not use Paxlovid in pregnancy or if breastfeeding • Use remdesivir if >12/40 gestation as per Adult Guideline indications with the same dosing as above • Remdesivir is compatible with breastfeeding
STEROIDS	Adults who meet **high risk criteria** AND are ineligible for antivirals AND are within 14 days of symptom onset	Consider inhaled budesonide 800micrograms BD for up to 14 days if respiratory symptoms • **Updated budesonide guidance available here** Do not use systemic steroids to treat COVID-19 without an oxygen requirement
	Adults without oxygen requirement, but another evidence-based indication for systemic steroids (e.g. asthma/COPD exacerbations)	Steroids as per usual practise
ANTIBODY THERAPY	Adults with **any severity of illness**	**Do not use casivirimab/imdevimab (Ronapreve)** due to lack of efficacy against Omicron, and negligible Delta variant transmission in New Zealand currently *Guidance about use in specific cases if advised by an expert clinician is available **here**.

Supportive Management: **all patients in hospital**

MODALITY	PATIENT SUB-GROUPS	RECOMMENDATION
RESPIRATORY SUPPORT	All patients	• Switch nebulisers to metered dose inhalers via spacer if possible • Monitor closely for worsening hypoxia if elevated work of breathing or respiratory rate
	SpO_2 <92% at rest	• Administer dry oxygen (1-4 L/min) via standard nasal prongs • Use Hudson mask (5-10 L/min), Venturi device or high flow nasal oxygen (HFNO) if required • Aim for SpO_2 92–96% (88–92% for those at risk of hypercapnic respiratory failure) • Encourage use of self-proning
	Unable to maintain SpO2 ≥92% on conventional oxygen or high flow nasal oxygen [HFNO] (requiring Fi02 >40%)	• Consider CPAP. Settings should be individualised, but a starting pressure of 8-10cm H_20 is common • Continue HFNO if CPAP unavailable, during meal breaks from CPAP or patient intolerance of CPAP • Encourage use of self-proning
	Hypercapnic patients with underlying COPD or OHS	• Consider BiLevel Non-Invasive Ventilation (NIV) in addition to above
	Pregnancy	• SpO2 target is ≥ 94%; ideally aim for 96-98%. • After 20/40 avoid positioning flat on back: use a wedge for lateral supine positioning. Left lateral during resuscitation or if hypotensive. • Self-proning may be possible (depending on gestation and habitus).
FLUID MANAGEMENT	• Assess for hypovolaemia and correct as required. • Avoid excessive resuscitation or 'maintenance' fluids • Anticipate and monitor ongoing fluid losses	
VTE PROPHYLAXIS	• ***All patients enrolled in ASCOT-ADAPT or REMAP-CAP (anticoagulation domains)***	• ***As per trial protocol***
	Hospitalised adults with: • mild COVID-19 • <u>OR</u> severe and critical COVID-19 <u>AND</u> no contra-indication to anticoagulation e.g. risk for major bleeding	Enoxaparin 40mg SC once daily (standard prophylaxis) • Adjust dose for impaired renal function (NB Therapeutic-dose anticoagulation is not beneficial and probably hazardous when initiated prophylactically in severe and critical COVID-19)
	Hospitalised adults with **moderate** COVID-19 <u>AND</u> no contra-indication to anticoagulation e.g. risk for major bleeding (NB moderate = *stable adult patient presenting with shortness of breath and/or reduction in resting oxygen saturation while breathing air. Able to maintain oxygen saturation ≥92% (or ≥90% for patients with chronic lung disease) with up to 4 L/min oxygen via nasal prongs*)	Therapeutic dose anticoagulation **should be considered** over standard prophylaxis for up to 14 days, or until clinical recovery (discharge or resolved hypoxia) Enoxaparin 1mg/kg SC twice daily (max 150mg BD) • Adjust dose for impaired renal function **All other patients should receive standard prophylaxis** as detailed above

	Hospitalised pregnant adults with mild OR severe/critical COVID-19 UNLESS: • Delivery expected within 24 hours (if only on enoxaparin 40mg SC once daily then 12 hourly) • Platelets < 50 • Actively bleeding / coagulopathy • Severe hypertension (>160/110)	Enoxaparin 40mg SC once daily (standard prophylaxis) • dose adjustment may be necessary if current weight ≥90kg
	Hospitalised pregnant or postpartum adults with moderate COVID-19 AND no contra-indication to anticoagulation (as above)	Consider therapeutic anticoagulation as for non-pregnant adults (above)
	Anticoagulation in pregnancy should be considered for a longer duration if post-partum or has additional risk factors for VTE (discuss with Obstetrics)	
INTENSIVE CARE	Regular, open and early discussions between ward-based clinicians and local ICU team is strongly encouraged. In addition to local referral guidelines, ICU review should be prompted by the following: • Significant oxygen requirement (e.g. requiring FiO2 of >40% to maintain SpO_2 >92%, or needing CPAP) • Increased work of breathing with impending respiratory failure • Haemodynamically unstable and / or hypotension not responsive to fluid bolus • Rapidly worsening tachypnoea or hypoxaemia Detailed clinical guidance for ICU care of COVID-19 is beyond the scope of this guideline	
ANTIBIOTIC THERAPY	Antibiotics should not be used to treat COVID-19 pneumonitis: bacterial co-infection is uncommon.	
	Severe/critical COVID-19 especially with any deterioration occurring >7 days post onset and/or >3 days after hospital admission	• Evaluate for secondary infection, including hospital-acquired infection • Discuss with local Infectious Diseases / Microbiology team if concern for secondary infection
COMMUNICATION & HOLISTIC CARE	Encourage fo all patients: • Clearly communicate typical symptoms and anticipated clinical course with patient, family/whānau or carers • Reinforce importance of complying with all Public Health messages, including self-isolation and testing • When possible, explain risks, benefits and likely outcomes of treatments with patients, family/whānau or carers • Use an interpreting service to assist communication if required • Facilitate regular clinical updates, and video calls between patient family/whānau or carers • Routinely refer to local cultural and/or spiritual support services • Consider early involvement of Palliative Care and/ or Liaison Psychiatry services to assist with symptom management, particularly anxiety, dyspnoea and delirium/agitation • Ensure appropriate housing, financial and social support is in place prior to discharge (including a working phone). If concerns, refer to social work • If welfare or cultural support issues identified, liaise with Public Health or Regional Isolation Quarantine (RIQ) according to regional processes as part of **discharge planning**	
	• Ensure Maternity services including lead maternity carer are alerted so wrap-around antenatal and post-natal care can be provided for the mother and baby	
THERAPIES FOR EXISTING INDICATIONS	• Nocturnal CPAP for Obstructive Sleep Apnoea (inpatients)	Consider changing usual vented CPAP mask to a non-vented mask + expiratory port + filter (decision depends on equipment availability and staff expertise)
	• ACE-inhibitors / ARBs	• Usual care (i.e. may be continued in COVID-19 unless otherwise contra-indicated)

	• Oral contraceptive pill (with or without oestrogen)	
	• Corticosteroids for asthma/COPD (inhaled or oral, with or without bronchodilators)	• Usual care • Do not use a nebuliser unless definite clinical need
	• Oral menopausal hormone therapy / HRT	• Consider stopping until after recovery
	• All pregnancy-related supplements and medications should be continued	
SURGERY	• Elective minor surgery should generally be deferred until at least four weeks, and major surgery until 8-12 weeks, following recovery from COVID-19 if patient outcome is not compromised • Acute surgical procedures that are indicated during active COVID-19 infection should be discussed with local ID and infection control services • Comprehensive preoperative and ongoing assessment must be carried out to ensure optimal clinical decision-making	
	• Caesarean section (including emergency) should not be deferred if clinically indicated, e.g. if needed for maternal resuscitation or immediate fetal concern; mode of delivery should otherwise remain based on obstetric indication	

COVID-19 Therapeutics: patients **requiring oxygen**

MODALITY	PATIENT SUB-GROUPS	RECOMMENDATION
STEROIDS	Adults with sustained oxygen requirement	Dexamethasone 6mg* daily PO/IV for 10 days OR until hospital discharge Do not routinely continue after discharge if completed 5 days in hospital *consider dexamethasone 12mg PO/IV once if would qualify for **immunomodulation**, but medication is unavailable within next 24 hours
	Pregnancy with sustained oxygen requirement to maintain SpO2 ≥94%	If steroids needed for fetal lung maturation (usually < 34^{+6} weeks): • dexamethasone 6mg IM every 12 hours for four doses • THEN either prednisone 40mg PO daily, OR hydrocortisone 80mg IV twice daily If steroids <u>not</u> required for fetal lung maturation, use non-fluorinated steroids: • prednisone 40mg PO daily OR hydrocortisone 80mg IV twice daily OR methylprednisolone 40mg IV once daily Total duration is 10 days total OR until discharge, whichever is sooner.
	Risk of **gestational diabetes:** monitor blood glucose levels closely and start treatment if elevated.	
ANTIVIRAL THERAPY	***All patients enrolled in ASCOT-ADAPT trial (anti-viral domain)***	***As per trial protocol & randomisation (in addition to remdesivir, if indicated below)***
	Adults with new sustained oxygen requirement within first 7 days of illness	• Do not start remdesivir • Complete course (3 days) if started earlier in illness

	Adults with COVID-19 after day 7 of illness	• Do not start remdesivir • Complete course (3 days) if started earlier in illness
	Adults with severe immunocompromise with any stage/severity of COVID-19	Discuss with local infectious diseases team
	Pregnancy (meeting the same clinical criteria as above)	• Use remdesivir if >12/40 gestation as per Adult Guideline indications with the same dosing as above • Remdesivir is compatible with breastfeeding
ANTIBODY THERAPY	Adults with **any severity of illness**	**Do not use casivirimab/imdevimab (Ronapreve)** due to lack of efficacy against Omicron, and negligible Delta variant transmission in New Zealand currently *Guidance about use in specific cases if advised by an expert clinician is available **here**.
IMMUNE MODULATION THERAPY	**In patients receiving systemic steroids in combination with immune modulation, we recommend screening for, and consider empiric treatment of latent infection, e.g. Hepatitis B or strongyloidiasis (in patients who have lived in an endemic region)**	
	There are no trials of immune modulation therapies currently recruiting in New Zealand	
	Adults with moderate COVID-19 • AND receiving systemic steroids • AND elevated CRP or other evidence of severe systemic inflammation OR clinically deteriorating • AND there is not another active, severe concurrent infection	Give baricitinib: • 4mg PO/NG daily for 14 days or until hospital discharge • Reduce to 2mg PO daily if eGFR 30-60mL/min • Reduce to 1mg PO daily if eGFR 15-29mL/min* • Do not use if eGFR <15mL/min • Avoid in pregnancy or breastfeeding • Baricitinib is a **section 29** product OR tocilizumab: • 8mg/kg IV (actual body weight) rounded to nearest 80mg or 200mg vial (max dose 800mg), as a single dose • *Notes: risk of secondary infection may be increased; CRP response is inhibited, and consequent reduction in CRP does not necessarily correlate with response to treatment* **baricitinib 2mg PO every 48 hours is an alternative*
	Adults with severe / critical COVID-19 requiring non-invasive or mechanical ventilation or organ support: • AND receiving systemic steroids • AND there is not another active, severe secondary infection	Give tocilizumab as above • Start as soon as possible if requiring NIV, mechanical ventilation or other organ support OR baricitinib, if tocilizumab is unavailable (as above). • If tocilizumab is available and baricitinib commenced earlier in illness, suggest change to tocilizumab Do not treat with both baricitinib and tocilizumab together
	COVID-19 not meeting the criteria above	Do not use immune modulation therapy
	Pregnancy (meeting the same clinical criteria as above)	Give tocilizumab (same dosing as above): • *Notes: Tocilizumab crosses the placenta after 28/40, but no evidence of harm to date. Suggest deferring live vaccination (i.e. Rotarix, BCG) up to 6 months in neonates with antenatal exposure. All other vaccinations are safe.* • *Compatible with breastfeeding.* • *May cause raised ALT and thrombocytopenia, mimicking pre-eclampsia / HELLP.* • *Do not use baricitinib (as above)*