COVID-19 Inpatient Medical Therapies Guideline

This Guideline should be utilised for adult patients (16 years and older) with suspected or confirmed COVID-19 who are admitted as an inpatient to Western Health.

For obstetric and neonatal guidelines, please see microsite for women and children: https://coronavirus.wh.org.au/clinical-guidelines/womens-childrens/

Version 13.0 updates and additions:

- **COVID therapies access criteria updated**
- **Remdesivir to be given only within the first 5 days of symptoms (including patients with moderate-severe COVID)**

Feedback and suggestions to james.molton@wh.org.au

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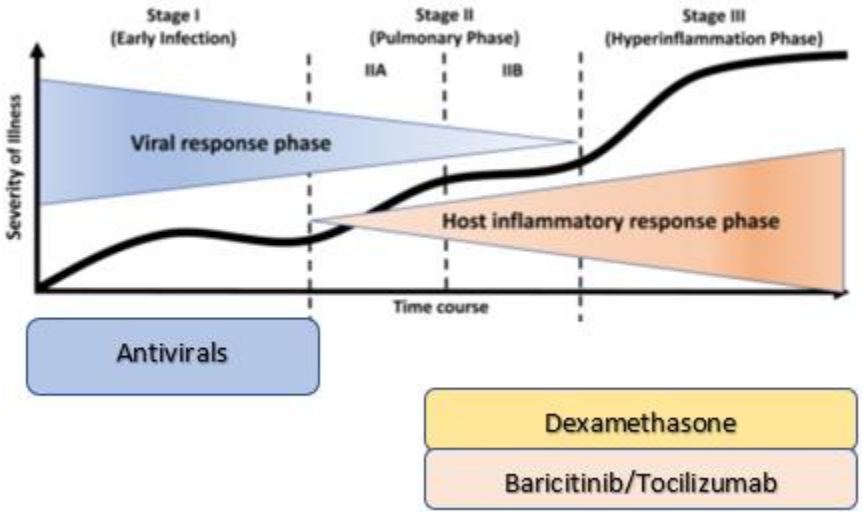
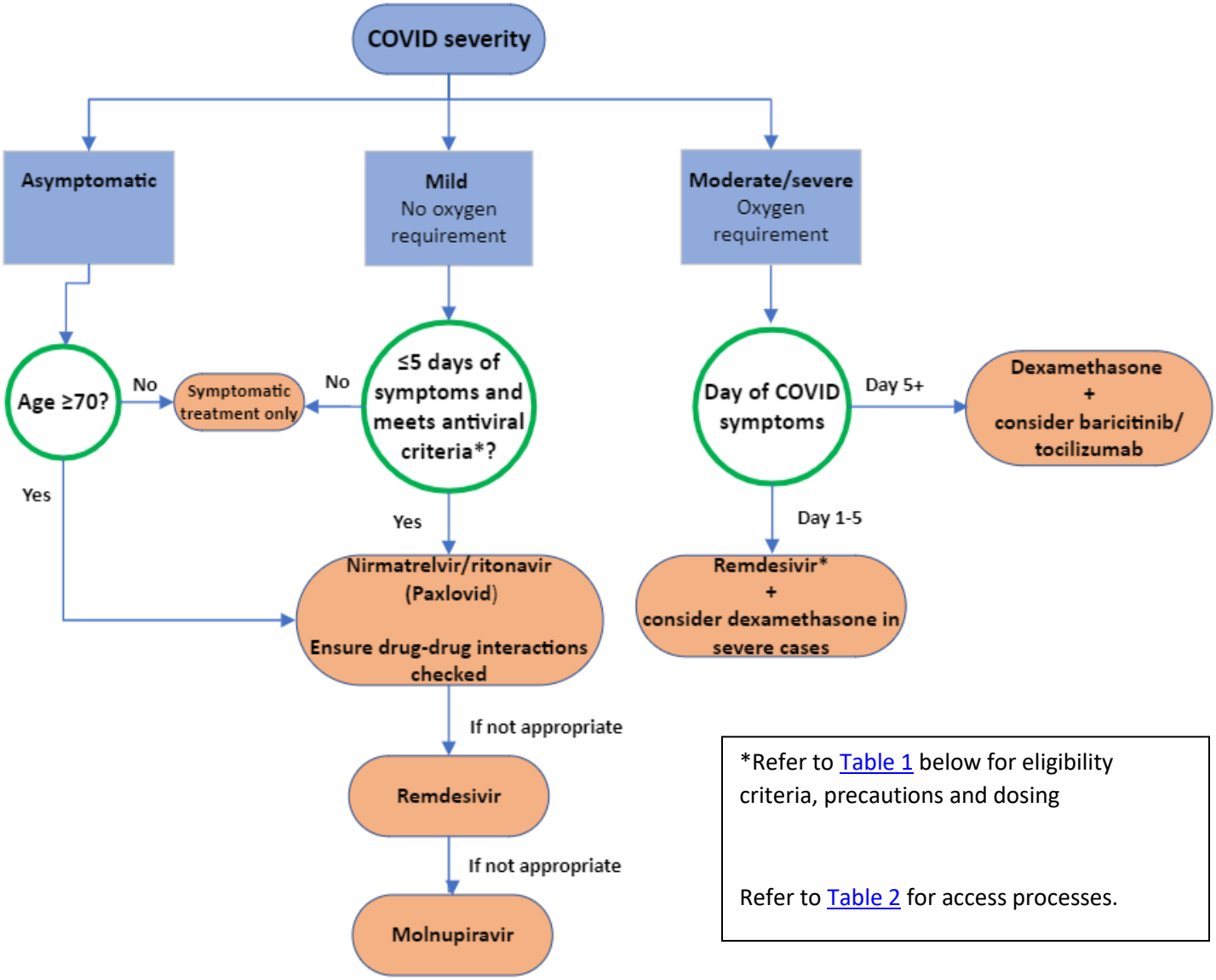
COVID natural history and timing of therapies



Initial Inpatient Management of COVID Flowchart



*Refer to Table 1 below for eligibility criteria, precautions and dosing

Refer to Table 2 for access processes.

Table 1: COVID therapies indications, eligibility and dosing

COVID therapy	Indications	Exclusions and precautions	Dosage

Nirmatrelvir/ ritonavir (Paxlovid)	**1. COVID-positive with mild illness and:**
	- No supplemental oxygen requirement
	- ≤ 5 days since symptom onset
	- At least one of:
	  ○ Age ≥70
	  ○ Immunocompromised
	  ○ Age ≥50 and a medical risk factor
	
	2. Asymptomatic COVID-positive patients aged ≥70
		Exclusion criteria:
		eGFR <30mL/min
		Severe hepatic impairment (Child-Pugh C)
		Age <12 years
		Age 12-17 years and weight ≤40kg
		
		Precautions:
		Paxlovid interacts with many other medications. A drug-interaction check must be performed using one of the following interaction checkers:
		- Liverpool COVID-19 Interactions (covid19-druginteractions.org)
		- Lexicomp® Drug Interactions - UpToDate
		
		Many patients can safely have interacting medications withheld or the dose reduced in order to be prescribed Paxlovid. Refer to Appendix 1 for advice.
			eGFR≥60mL/min:
			300mg/100mg PO 12-hourly for 5 days
			
			eGFR 30-60mL/min:
			150mg/100mg PO 12-hourly for 5 days
			
			Note:
			Outpatient dialysis patients may be started on PBS-funded Paxlovid at a reduced dose by the Renal team. This can be continued on admission to hospital.
			
			However, dialysis patients that need to start antiviral therapy as an inpatient should be commenced on remdesivir.

Remdesivir	**1. COVID-positive with mild illness and:**
	- ≤ 5 days since symptom onset
	- At least one of:
	  ○ Age ≥70
	  ○ Immunocompromised
	  ○ Age ≥50 and a medical risk factor
	
	2. COVID-positive with moderate-severe illness and:
	  ○ ≤ 5 days of symptom onset
	  ○ Saturations ≤ 92% on room air OR respiratory distress with use of accessory muscles of respiration
	
	3. Asymptomatic COVID-positive patients aged ≥70
		Exclusion criteria:
		Mechanical ventilation for greater than 48 hours at time of commencement
		
		Multi organ failure
		
		ALT ≥5 x ULN or ALT ≥3 x ULN and bilirubin ≥2 x ULN
		
		Age <12
		
		Age 12-17 and weight ≤40kg
		
		Note:
		Remdesivir can be safely used in patients with eGFR<30ml/min including those on dialysis
		
		(annotate the access form with 'eGFR<30 and clinically appropriate for remdesivir')
			Mild/asymptomatic illness:
			200mg IV on day 1 then 100mg IV daily for two days
			
			Moderate/severe illness:
			200mg IV on day 1 then 100mg IV daily for four days

Molnupiravir	**1. COVID-positive with mild illness and:** - No supplemental oxygen requirement - ≤ 5 days since symptom onset - At least one of: ○ Age ≥70	**Exclusion criteria:** Pregnant and breastfeeding Age <18 years **Precautions:**	800mg PO 12-hourly for 5 days

	○ Immunocompromised ○ Age ≥50 and a medical risk factor **2. Asymptomatic COVID-positive patients aged ≥70**	- Women should use effective contraception during treatment and for 4 days afterwards - Men should us barrier contraception during and for at least 3 months after treatment	
Dexamethasone	**COVID-positive and requiring supplemental oxygen**	**Precautions:** - Caution if within 5 days of illness onset - Strongyloides reactivation can occur. Check serology in at risk patients	6mg PO/IV daily for up to 10 days Cease on discharge
Baricitinib	**COVID-positive and requiring supplemental oxygen**	**Exclusion criteria:** - Neutrophils <1x10^9 /L - EGFR < 15 mL/min - ALT or AST > 5 x upper limit of normal - Pregnant or breastfeeding **Precautions:** - Caution if within 5 days of illness onset - Immunocompromised patients - Evidence of other active infection - Lymphocytes < 0.2 x 10^9/L	4mg daily for up to 14 days. Renal doses: eGFR 30 to <60 mL/min: 2mg daily eGFR 15 to < 30 mL/min: 2mg every second day Cease when the patient has clinically improved. Do not continue on discharge from hospital.
Tocilizumab	**COVID-positive patients requiring supplemental oxygen that:** - Have evidence of systemic inflammation (CRP≥75) - Are not suitable for baricitinib	**Exclusion criteria:** - ALT or AST > 10 x upper limit of normal - Neutrophils <0.5x10^9/L - Platelets <50x10^9/L - **Precautions:** - Caution if within 5 days of illness onset - Immunocompromised patients - Evidence of other active infection	Give a single dose. Weight-based dosing: >90 kg: 800 mg 66–90 kg: 600 mg 41–65 kg: 400 mg 30 - 40 kg: 8 mg/kg

Antibiotics in COVID:

Bacterial superinfection is unlikely early in infection, the risk increases over the course of infection. Antibiotics are not without harm and should be avoided early in illness and reserved for cases where bacterial superinfection is highly likely. Antibiotic use should be guided by procalcitonin.

Order procalcitonin (PCT) to guide duration (mark pathology order as 'urgent' for rapid turnaround):
PCT < 0.25 - cease antibiotics within 24h - bacterial superinfection unlikely
PCT 0.25 to 1.0 - cease antibiotics as early as possible if there is no evidence to support bacterial co-infection and PCT falling after admission.
PCT > 1 or doubling of PCT - complete treatment for CAP. Switch to oral antibiotics according to oral switch criteria.

Definitions of immunocompromise for access to antivirals

1. Any primary or acquired immunodeficiency including:

a. Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders,

b. Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months),

c. Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency

2. Any significantly immunocompromising condition(s) where, in the last 3 months the patient has received:

a. Chemotherapy or whole body radiotherapy,

b. High-dose corticosteroids (at least 20 mg of prednisone per day, or equivalent) for at least 14 days in a month, or pulse corticosteroid therapy,

c. Biological agents and other treatments that deplete or inhibit B cell or T cell function (abatacept, anti-CD20 antibodies, BTK inhibitors, JAK inhibitors, sphingosine 1-phosphate receptor modulators, anti-CD52 antibodies, anti-complement antibodies, anti-thymocyte globulin),

d. Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) including mycophenolate, methotrexate, leflunomide, azathioprine, 6-mercaptopurine (at least 1.5mg/kg/day), alkylating agents (e.g. cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus)

3. Any significantly immunocompromising condition(s) where, in the last 12 months the patient has received an anti-CD20 monoclonal antibody treatment, but criterion 2c above is not met

4. Others with very high-risk conditions including Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease and other haemoglobinopathies

5. People with disability with multiple comorbidities and/or frailty.

Risk factors for severe COVID

1. The patient is in residential aged care

2. The patient has disability with multiple comorbidities and/or frailty

3. Neurological conditions, including stroke and dementia and demyelinating conditions

4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease

5. Heart failure, coronary artery disease, cardiomyopathies

6. Obesity (BMI greater than 30 kg/m^2)

7. Diabetes type I or II, requiring medication for glycaemic control

8. Renal impairment (eGFR less than 60mL/min)

9. Cirrhosis

Table 2: Processes for accessing COVID therapies

Medication	Inpatients: During Pharmacy hours	Inpatients: After Pharmacy hours	Patient's being discharged from Emergency
Nirmatrelvir/ ritonavir (Paxlovid)	1. An interaction check must be performed using one of the following interaction checkers: - Liverpool COVID-19 Interactions (covid19-druginteractions.org) - Lexicomp® Drug Interactions - UpToDate. 2. Pharmacy will supply the medication during business hours.	1. An interaction check must be performed using one of the following interaction checkers: - Liverpool COVID-19 Interactions (covid19-druginteractions.org) - Lexicomp® Drug Interactions - UpToDate 2. The medication can be obtained by contacting the After Hours Administrator 3. Ensure the right prepack is selected for the patient's renal function (EGFR ≥ 60 – standard pack, eGFR ≥ 30 to < 60 – renally adjusted pack)	Patients discharging from Emergency can obtain oral antivirals through a PBS prescription. The script can be filled by Pharmacy during working hours. Patients can obtain oral antivirals from community pharmacies after hours. Oral Treatments | Find a Pharmacy can be used to locate pharmacies holding the medications – search for Paxlovid (nirmatrelvir/ritonavir) or Lagevrio (molnupiravir)
Molnupiravir	Pharmacy will supply the medication during business hours.	Available through the After Hours Administrator	
Remdesivir	An access form must be completed. Mild COVID: Request to Access Medication for Mild COVID-19 form. Moderate-Severe: Request to Access Remdesivir form 1. Email the form to: Sunshine: COVID19MedicationRequest-SH@wh.org.au Footscray: COVID19MedicationRequest-FH@wh.org.au 2. Inform the ward pharmacist that an application has been submitted 3. The Pharmacy Department will organise supply of remdesivir.	An access form must be completed. Mild COVID: Request to Access Medication for Mild COVID-19 form. Moderate-Severe: Request to Access Remdesivir form 1. Email the form to: Sunshine: COVID19MedicationRequest-SH@wh.org.au Footscray: COVID19MedicationRequest-FH@wh.org.au 2. Print a copy of the form and provide to the After Hours Administrator. The After Hours Administrator will provide the first dose. 3. The After Hours Administrator must leave the request form in the after hours cupboard for retrieval by Pharmacy. 4. Further doses of remdesivir will be dispensed by the Pharmacy Department the following day during business hours.	Refer to HITH. Consider prescribing oral antivirals if after hours or not accepted by HITH.
Dexamethasone	Available on imprest or from Pharmacy	Check the Global Imprest List for after-hours availability.	For patients requiring hospital admission. Cease on discharge.
Baricitinib	Available from Pharmacy	Available through the After Hours Administrator	For patients requiring hospital admission. Cease on discharge.
Tocilizumab	Available from Pharmacy	Available through the After Hours Administrator	N/A

Appendix 1: Management of common drug interactions with Paxlovid

Paxlovid has many drug interactions, primarily due to its ability to inhibit CYP enzymes and p-glycoprotein. Paxlovid is also metabolised by CYP enzymes and is liable to drug interactions with other CYP enzyme inducers/inhibitors.

Many drug interactions involving Paxlovid can be managed by withholding, dose reducing or monitoring the effects of the interacting medication. Some examples are provided in the table below.

Table 3: Management of select common drug interactions with Paxlovid

	Outcome of coadministration with Paxlovid	**Suggested management**
Simvastatin	Simvastatin levels greatly increased.	Consider withholding Simvastatin 12 hours prior to Paxlovid administration and until 3 days after Paxlovid course completed.
Rosuvastatin/Atorvastatin	Rosuvastatin/Atorvastatin levels increased	Consider withholding atorvastatin/rosuvastatin during Paxlovid administration. Atorvastatin/rosuvastatin can be recommenced the day after Paxlovid is finished.
Lercanidipine	Lercanidipine levels greatly increased.	Consider withholding lercanidipine 12 hours prior to Paxlovid administration and until 3 days after Paxlovid course completed. Monitoring of blood pressure can be performed during this period and an alternative antihypertensive considered.
Amlodipine/Felodipine	Amlodipine/Felodipine levels increased	For the duration of Paxlovid administration and 3 days after the course is finished, consider: - Withholding amlodipine/felodipine - Reducing the amlodipine/felodipine dose by half Monitoring of blood pressure can be monitored during this period and an alternative antihypertensive considered.
Clopidogrel	Clopidogrel levels decreased	**Do not use Paxlovid in patients taking clopidogrel that have been recently stented. Highest risk within 6 weeks of stenting.** Consideration can be given for using Paxlovid in patients taking clopidogrel in other clinical scenarios in which a loss of activity during the period of coadministration is not considered likely to cause harm.
Amitriptyline	Amitriptyline levels increased (weak interaction)	Monitor for adverse effects from amitriptyline until three days after Paxlovid ceased.

Before using interacting medications together consider:

- The nature of the interaction and potential consequences to the patient of changes in drug exposure

- The length of CYP inhibition of Paxlovid persists for 3-5 days after cessation. Restart withheld medications (or regular doses for dose reduced medications) 3-5 days after Paxlovid is ceased. Wait 5 days for narrow therapeutic index drugs or drugs extensively metabolised by CYP.

- Consider the half-life of the interacting medicine. How long must it be withheld before Paxlovid can safely be commenced? Will this delay the commencement of Paxlovid beyond day 5 of symptoms?

- For patients discharging from hospital: The ability for the patient to manage complicated changes to their regimens and whether their regular medications are packed into a dose administration aid by their local pharmacy that would need to be altered.