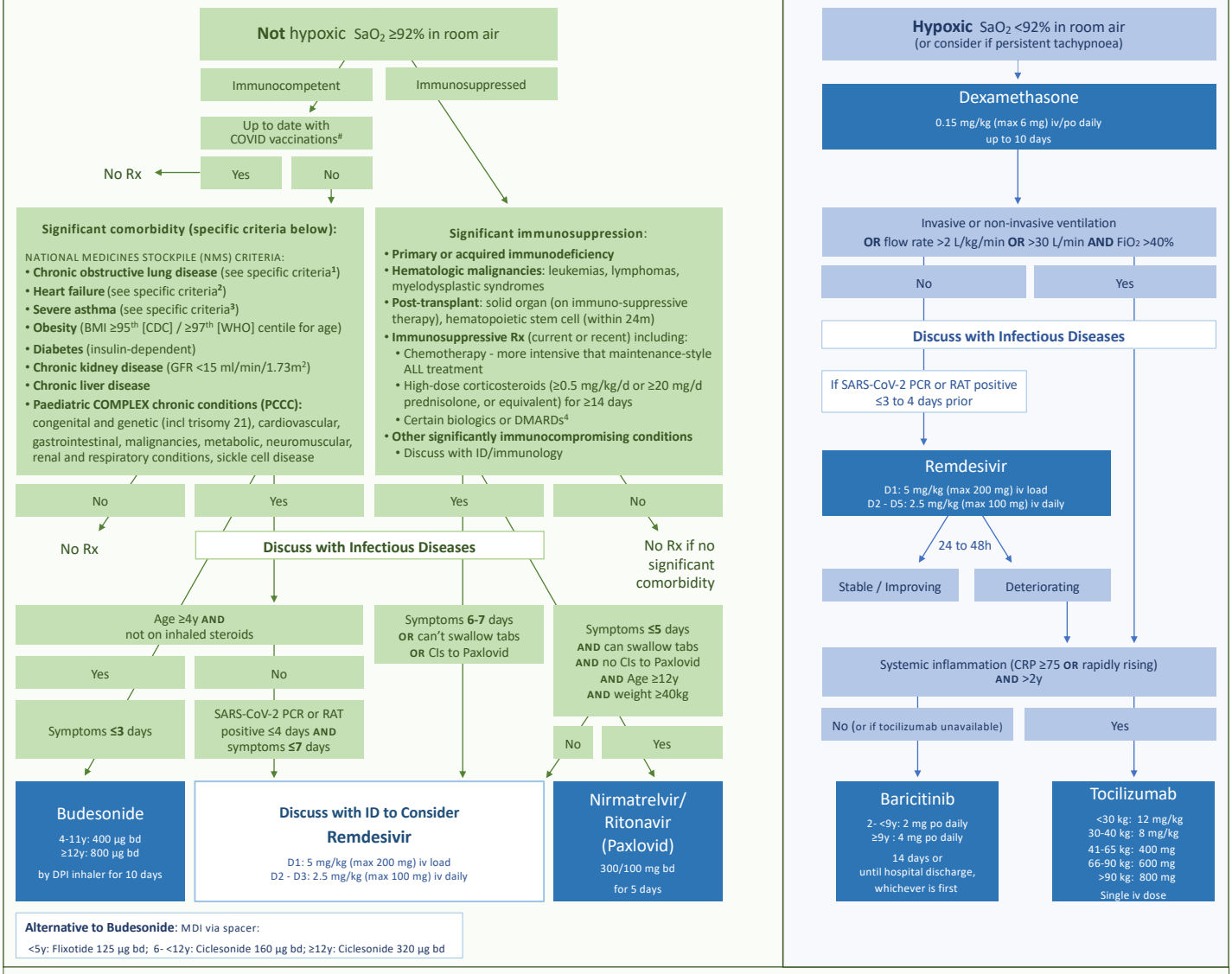
Algorithm for the Management of Children with **Symptomatic** COVID-19

The Royal Children's Hospital Melbourne



Specific criteria for significant comorbidity:

1 Chronic lung disease
- cystic fibrosis (or bronchiectasis) w FEV1 <60%
- congenital tracheal stenosis
- pulmonary hypertension Rx O_2
- neuromuscular disease (req resp support)
- tracheostomy requiring ventilation

2 Heart failure
- cardiomyopathy (req. diuretics)
- shunt-dependent circulation
- pulmonary hypertension (req specific Rx)
- single ventricle

3 Severe asthma fulfilling ANY of these criteria:
- in last 12m either of the following:
  ≥1 severe exacerbation req. ICU admission or iv treatment; **OR**
  ≥2 hospital admissions for asthma
- children req. biologic therapy for symptoms

4 Biologics or DMARDs
- Certain biologics or DMARDs that are expected to reduce COVID-19 vaccine response, including:
  Biologics: B-cell depleting or anti-CD52 monoclonal antibody, anti-thymocyte globulin;
  DMARDs: mycophenolate, methotrexate, azathioprine, calcineurin inhibitors

This algorithm provides a framework for decisions around the treatment of children with symptomatic COVID-19. This should be adapted for local use in line with institutional and governance requirements.

To be used only in conjunction with **COVID-19 medication guideline** document that details contraindications to be considered in all cases.

Drugs that are prescribed off label should have informed parent/guardian consent.

Thromboprophylaxis, infection control and supportive care are important in management but not included in this framework.

For definition of 'Up to date with COVID vaccinations', see ATAGI statement on defining 'up-to-date' status for COVID-19 vaccination | Australian Government Department of Health

Amanda Gwee, Hanna Holschier, Christine Plover and Nigel Curtis on behalf of RCH Infectious Diseases, **Version 6.0** Apr 2022

The Royal Children's Hospital Melbourne

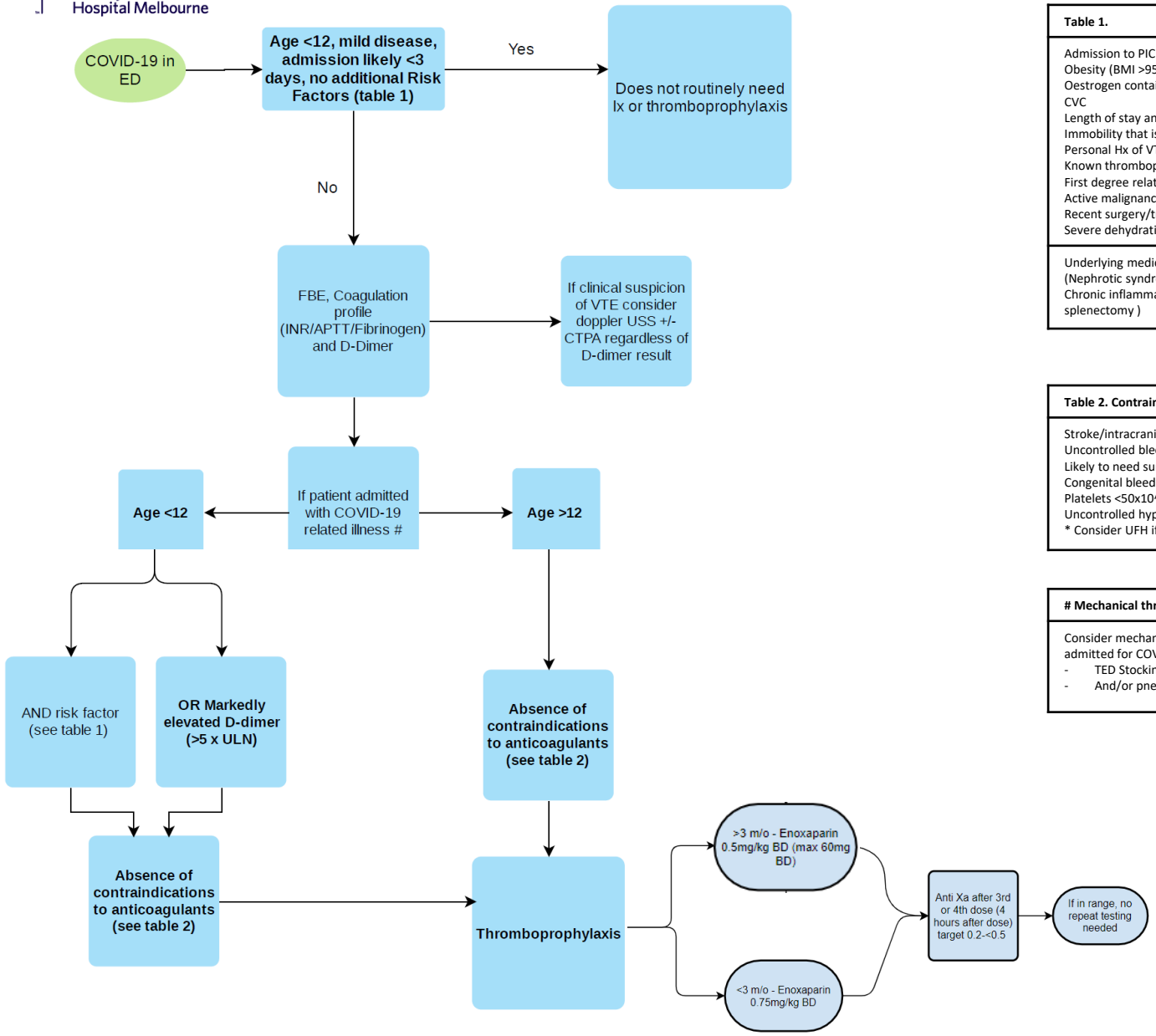


Table 1.

Admission to PICU
Obesity (BMI >95th Centile)
Oestrogen containing OCP
CVC
Length of stay anticipated > 3 days
Immobility that is not longstanding
Personal Hx of VTE
Known thrombophilia
First degree relative with VTE
Active malignancy
Recent surgery/trauma
Severe dehydration

Underlying medical condition
(Nephrotic syndrome, CF, Sickle cell disease, Cardiac disease, Chronic inflammatory disorder (eg JIA, IBD), post splenectomy)

Table 2. Contraindications to thromboprophylaxis

Stroke/intracranial haemorrhage
Uncontrolled bleeding
Likely to need surgery in <24/24
Congenital bleeding disorder
Platelets <50x10^9/L
Uncontrolled hypertension
* Consider UFH if CrCl <30ml/min

 # Mechanical thromboprophylaxis

Consider mechanical thromboprophylaxis for all patients admitted for COVID-19 reasons
- TED Stockings
- And/or pneumatic calf compressors

Anthea Greenway on behalf of RCH Clinical Haematology Version 2.0, Nov 2021

COVID-19 (SARS-CoV-2) Quick Medication Guide

Summary of therapy course depending on symptoms during hospitalisation

Please see the RCH guideline for management of symptomatic COVID for detailed information on when therapies are indicated.

Summary of disease modifying therapies

Dexamethasone

Eligible patients	<u>As per the algorithm</u> - Oxygen saturations (SaO_2) **<** 92% on room air - Oxygen saturation (SaO_2) ≥ 92% on room air **and** persistent tachypnoea (MET call criteria)
Dose	IV, oral: 0.15mg/kg (max 6mg) once daily for up to 10 days or until discharge (whichever is first)[1]
Notes	Give in the morning with food

Inhaled Budesonide (Pulmicort)

Inhaled budesonide has been shown to improve time to recovery with the chance of reducing prolonged hospital admissions in patients with confirmed SARS-CoV-2 who are at a higher risk of further complications.

Studies have only been performed in adult patients; however, it is recommended to consider utilising inhaled budesonide for the treatment of symptomatic SARS-CoV-2 in children and adolescents who do not require oxygen and who may be at high risk for disease progression.

Eligible patients	<u>As per the algorithm</u> - Patients with a significant co-morbidity (outlined in the algorithm) - High-risk groups (outlined in the algorithm) who have had symptoms for ≤ 3 days and NOT on inhaled corticosteroids
Non-eligible patients	Patients already on inhaled corticosteroids
Dose	4 to 11 years old: Inh 400mcg twice daily via dry powder inhaler (DPI)[7] ≥ 12 years of age: Inh 800mcg twice daily via dry powder inhaler (DPI)[2]
Contraindications	Patients unable to appropriately inhale from a DPI. Inhaled budesonide only comes in the DPI form in Australia and requires the ability to properly deeply inhale via the device for proper drug disposition into the lungs. If patients are unable to inhale from DPI, use:

	< 5 years: fluticasone 125 mcg twice daily via MDI +/- spacer 6 to 11 years: ciclesonide[9] 160 mcg twice daily via MDI +/- spacer ≥ 12 years: ciclesonide[9] 320 mcg twice daily via MDI +/- spacer
Notes	Rinse mouth out after use to minimise risk of developing oral candidiasis.

Remdesivir (Veklury)

Remdesivir is a nucleoside analogue prodrug, which has inhibitory effects on pathogenic animal and human coronaviruses, including SARS-CoV-2 (COVID-19).

Indication for use for patients ≥ 12 years of age <u>and</u> for patients weighing ≥ 40kg	<u>As per the algorithm</u> - Patients requiring non-invasive ventilation **or** flow rate >30L/min and FiO_2 > 40% (REMAP CAP) - Immunocompromised patients who have had a positive SARS-CoV-2 PCR or rapid antigen test (RAT) ≤ 3-4 days prior AND symptoms ≤ 7 days prior and are considered VERY high risk (initiation of remdesivir in this population will occur in consultation with the ID team)
Indication for use for patients < 12 years of age <u>and/or</u> for patients weighing < 40kg	Use of remdesivir for children or adolescents with COVID-19 outside of a trial setting should not be considered routine treatment. However, if treatment is considered in exceptional circumstances, it should be in direct consultation with the relevant stake-holders[3] and the exceptional circumstances and approving clinicians documented on the NMS request form.
Inclusion Criteria for patients ≥ 12 years of age and ≥ 40kg (all must apply before remdesivir access can be granted)	Current **inclusion** criteria as per the NMS include (all MUST apply); - Informed consent has been provided by the patient, or patients legal guardian - Age ≥ 18 years of age, **or** aged ≥ 12 and ≤ 18 years of age and weighing ≥ 40 kg. - Hospitalised with confirmed SARS-CoV2 or known contact with a confirmed case with syndrome consistent with COVID-19 awaiting confirmation by diagnostic testing - Oxygen saturation (SaO_2) ≤ 92% on room air **and** requiring supplemental oxygen - Alanine aminotransferase (ALT) < 5 x upper limit of normal (ULN) by local laboratory measure and/or ALT < 3 x ULN and bilirubin < 2 x ULN - EGFR > 30ml/min and not on dialysis or continuous veno-venous haemo-filtration
Exclusion Criteria	Current **exclusion** criteria include:

	- Evidence of multi-organ failure including but not limited to coagulopathy (significant thrombocytopenia), hepatic failure (elevated bilirubin) or renal failure (low urine output or estimated glomerular filtration rate (eGFR) <30ml/min) or significant cardiomyopathy (low cardiac output) - Renal failure requiring dialysis or continuous veno-venous haemo-filtration) - Mechanical ventilation for longer than 48 hours **at time** of application - Receiving extracorporeal membrane oxygenation (ECMO) - Known hypersensitivity to the study drug, the metabolites, or formulation excipient	
Precautions/Adverse Effects	Post-marketing reports; - Bradycardia; including severe bradycardia which can be fatal has been reported in patients receiving remdesivir for SARS-CoV2 - Mild-moderate increase of serum alanine aminotransferase and increased aspartate aminotransferase has been reported in patients receiving remdesivir for SARS-CoV2	
Dose for patients ≥ 12 years of age <u>and</u> ≥ 40kg	IV: 200 mg loading dose on day 1, followed by 100 mg daily for a further 3 - 5 days [10]	
Dose for patients < 12 years of age <u>and/or</u> < 40kg	3.5 kg to <40kg: IV: 5 mg/kg loading dose on day 1, followed by 2.5 mg/kg/dose once daily for a further 3 - 5 days[10] **As of today, there is no clear route to access remdesivir for patients in this age group. Once access is confirmed, this will be updated accordingly.**	
Dose adjustment for renal impairment (based on eGFR)	≥ 30 mL /min/1.73m^2	No dose adjustment required
	< 30 mL/min/1.73m^2	Remdesivir is not indicated in patients with renal impairment. Patient will be excluded for accessing remdesivir.
Dose adjustment for hepatic impairment	- Not recommended in patients with hepatic impairment (criteria above outlined). Patient will be excluded from accessing remdesivir. - If hepatic impairment develops in patients treated with remdesivir (elevation of ALT and/or signs of liver inflammation), discontinue remdesivir treatment	
Administration	Please refer to the Paediatric Injectable Guideline (PIG) or Australian Injectable Drug Handbook (AIDH) on appropriate dilution and administration information	

Drug access (patients ≥ 12 years of age and≥ 40kg)	Access to remdesivir is through the National Medicines Stockpile. Please refer to the "Request to Access Remdesivir" form for further information.
Drug access (patients < 12 years of age and/or < 40kg)	**Access to remdesivir via NMS in exceptional circumstances must be applied for using the 'Exceptional Circumstances' box on the NMS Request form with approval by ID consultant + specialty consultant**
RCH Approval	ID Consultant Approval Required + treating specialist if < 12 years
Notes	- Initial supply of remdesivir from the NMS will be for 5 days only. If a 10-day course is required, a subsequent application to the NMS for remdesivir will be required. A 10-day course MUST be approved by the appropriate clinicians. - The remdesivir formulation contains the excipient SBECD which accumulates in patients with kidney dysfunction, so patients with known kidney dysfunction will be excluded from remdesivir therapy.

Nirmatrelvir & Ritonavir (Paxlovid)

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro); inhibition of Mpro prevents processing of polyprotein precursors, resulting in inhibition of viral replication. Ritonavir is a pharmacokinetic enhancer, it inhibits CYP3A-mediated metabolism of nirmatrelvir, resulting in increased nirmatrelvir plasma concentrations. Ritonavir has no activity against SARS-CoV-2.[1]

Presentation	Nirmatrelvir; Tablet; 150 mg x 2 (pink) Ritonavir; Tablet; 100 mg (white)
Indication for use for patients ≥ 18 years of age	- Confirmed SARS-CoV-2 infections - No oxygen requirement
Indication for use for patients ≥12 years and <18 years of age and for patients weighing ≥ 40kg	- Confirmed SARS-CoV-2 infections - No oxygen requirement - Therapy is deemed appropriate via the RCH Covid-19 treatment algorithm and approval has been given by two specialists (one must be an Infectious Diseases (ID) Consultant), and one senior pharmacist
Indication for use for patients <12 years of age and for patients weighing and/or <40kg	No dosage recommendation is available for this age group. **Patients will not qualify for use.**

Inclusion Criteria (all must apply before Paxlovid access can be granted)	- Patient must be within day 0-5 of symptom onset from SARS-CoV-2 - Must meet one of the appropriate "Patient Access Groups" outlined on the NMS form and the corresponding immunosuppressed syndromes
Exclusion Criteria	- Patients <12 years of age - Patients <40kg - Patients unable to swallow tablets whole. Tablets CANNOT be crushed and given via feeding tubes. - Known hypersensitivity to either active ingredient (nirmatrelvir or ritonavir) - Any known severe drug-drug interactions (pharmacist review required of all patients initiated) - Significant renal impairment (eGFR < 30mL/minute) - Significant hepatic impairment (Child-Pugh class C) - Patients on other ritonavir containing regimens.
Precautions/Adverse Effects	- **Hepatic effects;** use of Paxlovid may lead to elevations of hepatic transaminase, clinical hepatitis and jaundice. Care should be taken when utilised in patients with known mild hepatic impairment - **Renal impairment;** accumulation of nirmatrelvir is increased in patients with renal impairment. Adjust dose as per recommendations below and monitor renal function. - **Drug-drug interactions;** there are a **large** number of interactions with Paxlovid and other medications. A pharmacist will need to be consulted on appropriateness of Paxlovid in patients on concomitant medications to ensure appropriateness of therapy. - **Patients with HIV;** for patients with uncontrolled or undiagnosed HIV-1 infection, there is a risk of HIV-1 protease inhibitor resistance (ritonavir is a HIV-1 protease inhibitor). Specialist referral is recommended.
Dose for patients ≥18years of age and ≥ 40kg	Oral; Take TWO (2) tablets of nirmatrelvir and ONE (1) tablet of ritonavir TWICE a day for FIVE days.
Dose for patients ≥12 years of age and ≥40kg	Oral; Take TWO (2) tablets of nirmatrelvir and ONE (1) tablet of ritonavir TWICE a day for FIVE days.

	For patients in this age bracket, specialist approval is required. Two senior clinicians (one **must** be an ID Consultant) will need to give approval prior to supply. The National Medicines Stockpile (NMS) form will need to be annotated with this detail.	
Dose for patients <12 years of age <u>and/or</u> <40kg	Not recommended. Paxlovid will not be supplied to patients in this age or weight bracket.	
Dose adjustment for renal impairment (based on eGFR)	**eGFR ≥ 60mL/min**	No dosage adjustment recommended. Dosage as above.
	eGFR ≥30 to <60mL/min	Nirmaltrelvir 150mg (1 tablet) and ritonavir 100mg (1 tablet) TWICE daily.
	eGFR <30mL/min	Use is not recommended.
Dose adjustment for hepatic impairment	**Mild or mod impairment (Child-Pugh class A or B);**	No dosage adjustment necessary
	Severe impairment (Child-Pugh class C)	Use is not recommended
Administration	Patients to swallow tablet whole. DO NOT crush or chew medication	
Drug access (patients ≥ 12 years of age <u>and</u> ≥40kg)	All supply of Paxlovid is via the NMS. The NMS criteria must be adhered for all patients who are referred for Paxlovid therapy. Pharmacists will thoroughly review patients prior to initiating Paxlovid therapy to review other medications and the possible risks of interactions.	
RCH Approval	ID Consultant approval + Senior Clinician + Pharmacist For patients ≥12 years of age and ≥40kg, two specialists from RCH will need to be consulted prior to initiation of Paxlovid therapy. One of these clinicians will need to be an ID specialist. An experienced pharmacist will review the patient's medication history and must also approve the prescribing.	
Interactions	**There are a number of <u>significant</u> drug-drug interactions with Paxlovid. Please be aware there are a number of <u>contraindications</u> with certain medications, including medication *which have been ceased* in the last 14 days.** **Supply of Paxlovid will only occur, after thorough review from an experienced pharmacist.** **A searchable database of interactions is found here:**	

	https://covid19-druginteractions.org/checker **NB: This database is still not comprehensive and is NOT an exhaustive list of interacting medications. Pharmacy review is required before supply can occur.**

Tocilizumab

Tocilizumab (Actemra) binds to and inhibits the activity of interleukin-6 (IL-6). In critically ill patients with SARS-CoV-2, tocilizumab may decrease the hyper-inflammation associated with SARS-CoV-2 and possibly improve overall outcomes.

As of the 17th August 2021, there is a significant shortage of tocilizumab within Australia and as a result its use is significantly restricted to ensure appropriate supply for its TGA-approved indications. As a result, in patients who are receiving supplemental oxygen but are not mechanically ventilated, baricitinib should be considered instead of tocilizumab, unless contraindicated.

Indication for use	Consider tocilizumab **in addition** to dexamethasone[4,5] in patients who are hospitalised with COVID-19 who require supplemental oxygen **and** where there is evidence of systemic inflammation.
Inclusion Criteria	As per the algorithm; - Deteriorating hospitalised patients on dexamethasone with confirmed SARS-CoV-2 infection who have signs of systemic inflammation (CRP ≥ 75 or rapidly rising)
Exclusion Criteria	Current **exclusion** criteria include: - Known hypersensitivity to tocilizumab. - Severe hepatic impairment (ALT/AST > 10 x ULN) - Patients with active, severe infections (excluding SARS-CoV2). o Tocilizumab has a significant warning for the risk of serious infections due to its immune supressing effects, this includes tuberculosis and other opportunistic infections. Extreme care should be taken when utilising tocilizumab in patients with active infections (viral, bacterial or fungal).
Precautions	Tocilizumab causes immune system suppression so should be used in caution in immunocompromised patients
Dose	For patients > 2 years of age - Patients < 30kg: 12mg/kg IV stat for ONE dose - Patients 30-40kg: 8mg/kg IV stat for ONE dose - Patients 40 to 65kg: 400mg IV stat for ONE dose - Patients 65 to 90kg: 600mg IV stat for ONE dose - Patients > 90kg: 800mg IV stat for ONE dose

Dose adjustments in renal impairment (based on eGFR)	No dosage adjustment required in renal impairment.
Dose adjustments in hepatic impairment	Not recommended in patients with active hepatic disease or hepatic impairment, described as ALT/AST > 10 x ULN.
Administration	Please refer to the Paediatric Injectable Guideline (PIG) or Australian Injectable Drug Handbook (AIDH) on appropriate dilution and administration information
Drug Access	Access to tocilizumab is through the National Medicines Stockpile. Please refer to the "Request to Access Tocilizumab" form for further information.
RCH Approval	ID Consultant Approval Required
Notes	Though the literature does support a second dose of tocilizumab > 8 hours post the initial dose if no shown improvement, due to the significant shortage in tocilizumab a secondary dose may not be able to be sourced.

Baricitinib (Olumiant)

Baricitinib (Olumiant) is a Janus kinases 1 and 2 inhibitor. Baricitinib, through its inhibitory mechanism, may decrease hyper-inflammation associated with SARS-CoV-2 and may improve overall outcomes.

Due to the significant shortage of tocilizumab (Actemra), baricitinib has received conditional approval from the Australian National COVID-19 Taskforce and the TGA to be utilised for hospitalised patients with COVID-19 who require supplemental oxygen.

Indication for Use	Consider baricitinib **in addition** to dexamethasone[6] in patients who are hospitalised with COVID-19 who require supplemental oxygen **and** are deteriorating
Inclusion Criteria	As per the algorithm - Deteriorating hospitalised patients on dexamethasone with confirmed SARS-CoV-2 infection - Deteriorating hospitalised patients on dexamethasone with confirmed SARS-CoV-2 infection who have signs of systemic inflammation and unable to access tocilizumab
Exclusion Criteria	Current **exclusion** criteria include: - Known hypersensitivity to baricitinib - < 2 years of age - Patients with active, severe infections (excluding SARS-CoV2) ○ Baricitinib has a significant warning for the risk of serious infections due to its immune supressing effects, this includes tuberculosis and other opportunistic infections. Extreme care should be

<table>
<tr><td></td><td colspan="2">taken when initiating baricitinib in patients with active infections (viral, bacterial or fungal)</td></tr>
<tr><td>Precautions</td><td colspan="2">Baricitinib causes immune system suppression so should be used in caution in immunocompromised patients.

Cytopenia may occur during treatment with baricitinib, recommended to avoid or cease treatment in patients who have[7];
- Lymphocyte count < 0.5 x 10^9 cell/L
- Haemoglobin < 80g/L
- Absolute neutrophil count < 1 x 10^9 cells/L

Care should be given when initiating in patients with renal impairment, dose adjustment will be required (see below).</td></tr>
<tr><td>Dose</td><td colspan="2">< 2 years of age: Not recommended and no dosage information available.
2 to < 9 years of age: PO 2mg daily for 14 days or until hospital discharge, whichever is first[7]
9 years of age to adult: PO 4mg daily for 14 days or until hospital discharge, whichever is first[7]</td></tr>
<tr><td rowspan="6">Dose adjustments for renal impairment (based on eGFR)</td><td rowspan="2">≥ 60ml/min/1.73m^2</td><td>2 to < 9 years: PO 2mg daily</td></tr>
<tr><td>9 years to adult: PO 4mg daily</td></tr>
<tr><td rowspan="2">30 to 60ml /min/1.73m^2</td><td>2 to < 9 years: PO 1mg daily</td></tr>
<tr><td>9 years to adult: PO 2mg daily</td></tr>
<tr><td rowspan="2">15 to <30ml/min/1.73m^2</td><td>2 to < 9 years: Not recommended.</td></tr>
<tr><td>9 years to adult: PO 1mg daily</td></tr>
<tr><td>< 15ml/min/1.73m^2</td><td>Not recommended.</td></tr>
<tr><td>Dose adjustments for hepatic impairment</td><td colspan="2">No dosage adjustment recommended.
However, if baricitinib induced liver injury is suspected, cease treatment immediately.</td></tr>
<tr><td>Administration</td><td colspan="2">- HAZARDOUS medication, appropriate PPE required when handling.
- Gloves when handling intact tablets and patients can swallow whole.
- Gloves, gown, N95 and eye protection when dispersing tablets.
- For patients unable to swallow whole tablets; disperse tablets in 10ml of sterile water for injection (WFI). Tablet should disperse in less than 5 minutes. Give immediately. Medication may be administered by gastrostomy feeding tubes and nasogastric feeding tubes. There is no evidence for jejunal administration, so do not administer by naso-jejunal or jejustomy feeding tubes[8]</td></tr>
</table>

Drug Access	Medication accessed via RCH pharmacy department. Patients must satisfactorily meet the above inclusion criteria and have approval before supply will be granted.
RCH Approval	ID consultant approval required
Notes	Medication is under constrained supply. All doses supplied that are not utilised (blister pack intact) should be returned to pharmacy.

Sotrovimab

Sotrovimab is a monoclonal antibody therapy that has been given provisional approval for the use in mild-to-moderate SARS-CoV2 infected patients who may be at a higher risk of progressing to severe complications from the infection.

Sotrovimab is currently still an investigational product, so long term safety and efficacy in patients with COVID-19 continues to be evaluated.

As of April 2022, Sotrovimab therapy is no longer indicated for the current variant of Omicron (B.A.2) due to reduced neutralising activity against this strain. It will not be recommended as therapy for patients with SAR-CoV-2 at RCH until further notice.

Casirivimab and Imdevimab (Ronapreve)

Casirivimab and imdevimab are two recombinant monoclonal antibodies formulated together to target the spike protein of SARS-CoV-2 to inhibit infection of host cells. It has been provisionally approved in Australia for both treatment and post-exposure prophylaxis of COVID-19.

Ronapreve is no longer available via the NMS so is no longer a therapy available to patients with SARS-CoV-2.

Version 2.4

Compiled & written by Hanna Holschier (RCH PICU Pharmacist) & Christine Plover (RCH Medicines Information Pharmacist) 19/4/22

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RCH PIMS-TS/MIS-C Guideline

Key Points

- Consider PIMS-TS in a febrile child with any of the following:
    - rash
    - conjunctival injection
    - abdominal symptoms (pain, vomiting, diarrhoea)
    - features of shock (tachycardia and/or hypotension for age)
- Early recognition of a child with possible PIMS-TS improves outcomes
- Children with PIMS-TS require a multidisciplinary team approach – initial referral should be made to the Infectious Diseases team
- Investigations and empiric therapy for sepsis and/or toxic shock syndrome should be commenced while MDT being arranged to discuss need for specific therapies (IVIG and/or steroids)

Background

Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS), also known as Multisystem Inflammatory Syndrome in Children (MIS-C) is a novel, rare post-infectious syndrome that occurs in those with previous SARS-CoV-2 infection.

- It occurs 2-4 weeks after acute COVID-19
- The preceding acute COVID-19 illness may be mild or asymptomatic
- The median age of patients is 9 years but has been described from infancy to mid-adulthood
- It is more common in
    - non-European Caucasian race/ethnicity
    - boys
    - those who are overweight or have obesity

Diagnosis

- The diagnosis is made on clinical and laboratory criteria, which are variably present
- There is no diagnostic test
- Early recognition is key

Appropriate investigations and prompt discussion with a multi-disciplinary team (including Paediatric Infectious Diseases, Rheumatology, General Paediatrics, Immunology, Haematology, Cardiology, Intensive Care as available) is essential. The initial referral should be made to the Infectious Diseases team.

The severity of PIMS-TS varies from mild disease to fulminant life-threatening shock and organ dysfunction. The clinical phenotype of PIMS-TS varies with age and is heterogeneous. Fever and evidence of systemic inflammation are typical.

Three over-lapping clinical phenotypes have been observed and may occur at any age (adapted from Schlapback LJ et al 2021).

(i) **Kawasaki disease (KD)-like phenotype** (often fulfilling AHA diagnostic criteria for complete or incomplete KD) is more common in children aged less than 5 years. Typical features include:

- fever
- polymorphous non-blanching rash
- mucosal involvement
- non-purulent conjunctival injection
- peripheral oedema
- cervical lymphadenopathy (can present as stiff, painful neck)
- coronary artery dilatation or aneurysms may be evident on echocardiography.

(ii) **Shock-like presentation** is more common in those over 5 years and characterised by:

- GI symptoms and signs (abdominal pain, diarrhoea, vomiting)
- distributive shock (due to myocardial dysfunction)
- polymorphous rash
- headache
- altered conscious state.
- coronary artery dilatation or aneurysms may be evident on echocardiography

(iii) **Undefined inflammatory presentation** is more common in children aged over 5 years, and is characterised by:

- persistent fever
- abdominal pain
- no cardiac involvement or shock
- other signs of PIMS-TS may be variably present (rash, conjunctival injection, peripheral oedema, cervical lymphadenopathy)
- may progress to more severe disease or resolve, even without treatment.

Case Definition

Note this definition is designed principally for research and surveillance purposes and should not be used to exclude the diagnosis.

Children and adolescents (< 18 years of age) with fever ≥3 days

AND two or more of the following:

a) Rash *or* bilateral non-purulent conjunctivitis *or* muco-cutaneous inflammation signs (oral, hands or feet)
b) Age-specific hypotension *or* 'shock' within 24 hours of presentation
c) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings *or* elevated Troponin/NT-proBNP)
d) Evidence of coagulopathy (by PT, PTT, elevated d-dimers)
e) Acute gastrointestinal problems (diarrhoea, vomiting or abdominal pain).

AND Elevated markers of inflammation such as CRP, procalcitonin.

AND Exclusion of other infectious causes of inflammation, including bacterial sepsis, toxic shock syndrome (note that treatment for PIMS-TS may need to be commenced before alternative diagnoses are definitively excluded)

AND Evidence of current or recent SARS-CoV-2 infection (RT-PCR, rapid antigen test or serology), or confirmed contact with COVID-19 case.

Note: results of testing may be delayed, particularly serology. If all other criteria are met, a diagnosis of PIMS-TS may be made with expert advice, and treatment initiated.

Assessment

History

- New symptoms can present sequentially over several days, thus history should include asking about diagnostic features that may have resolved by the time of presentation

Examination

- Findings can present sequentially over a number of days, thus careful daily examination is important
- Examine for features consistent with PIMS-TS and to exclude complications or alternative diagnoses (Table 1)
- Features of cardiovascular dysfunction – refer to sepsis guideline
- Features of toxic shock syndrome – may include fever, vomiting, diarrhoea, myalgia, conjunctival injection, confusion, collapse and a widespread erythematous rash

Table 1. Symptoms and signs suggestive of PIMS-TS

General	• Fever
Gastrointestinal	• Abdominal pain • Diarrhoea, vomiting (can mimic appendicitis)
Cardiovascular	• Chest pain • Tachycardia for age • Hypotension, shock, oliguria
Respiratory	• Cough, sore throat, respiratory distress • Hypoxia
Dermatologic	• Conjunctivitis, periorbital swelling/redness • Mucous membrane changes • Rash • Lymphadenopathy • Swollen hands/feet
Neurologic	• Headache, confusion, irritability • Reduced level of consciousness • Syncope

Differential Diagnoses

- Sepsis
- Toxic shock syndrome
- Acute abdomen, e.g. appendicitis
- Malignancy
- Haemophagocytic lymphohistiocytosis
- Systemic onset juvenile idiopathic arthritis

Management

Principles

All children with suspected PIMS-TS should have:

- Review by a senior clinician
- Early involvement of Multi-disciplinary Team; Infectious Diseases, Rheumatology, General Paediatrics and Immunology teams to guide initial management with Cardiology, Haematology and Intensive Care input as required. The initial referral should be made to the Infectious Diseases team.
- Blood cultures taken prior to commencing empiric broad spectrum antimicrobials as per RCH sepsis guidelines
- Regular observations and three-lead ECG monitoring
- If the child is profoundly ill or has signs of sepsis treat accordingly and involve ICU early as per sepsis guidelines

Investigations

Bloods

- Venous blood gas
- FBE, UEC, LFT, CRP, ESR
- Blood culture
- Coagulation profile, D-Dimer
- Ferritin, LDH, CK
- Troponin
- SARS-CoV-2 serology
- Serum to store (prior to any IVIG)
- Consider according to clinical presentation:
    - CMP, triglycerides, pro-BNP, procalcitonin (if in ICU)

Other investigations

- Respiratory PCR including SARS-CoV-2
- Chest X-ray – assess for cardiomegaly
- ECG – arrythmia, heart block
- Echocardiography – urgent if clinical instability or treating for PIMS-TS/KD
    - Myocardial dysfunction, pancarditis

Consider

- Abdominal ultrasound – if concerns of acute abdomen
- Neuroimaging – if concern reading neurological status

Table 2. Investigations consistent with PIMS-TS

Inflammatory and other biomarkers	• Elevated CRP • Elevated ESR • Elevated ferritin • Elevated procalcitonin • Elevated creatinine kinase • Elevated lactate dehydrogenase
Haematology	• Lymphopaenia • Neutrophilia • Thrombocytopaenia • Elevated D-dimer • Elevated fibrinogen
Cardiovascular	• Elevated troponin • Elevated pro-BNP • Myocardial dysfunction • Pericardial effusion
Gastrointestinal	• Abnormal liver function tests • Hypoalbuminaemia • Colitis/ ileitis • Ascites
CXR / CT scan	• Patchy infiltrates • Pleural effusion

Treatment

Supportive care

- Fluid resuscitation if signs of shock – caution if features of myocardial dysfunction due to risk of pulmonary oedema - see sepsis guideline
- Strict fluid balance chart
- Gastric protection (eg. omeprazole) for children receiving steroids

Antimicrobials

- All children with suspected PIMS-TS should be covered with broad-spectrum antimicrobials (IV ceftriaxone and IV flucoxacillin) after blood cultures are collected
- See sepsis guideline

Anti-inflammatory

- Anti-inflammatory treatment should be initiated following discussion with a multidisciplinary team once a diagnosis of PIMS-TS is made.
- Options for initial treatment are IVIG or steroids, or both
- Treatment should be tailored depending on the age of the child, clinical features and investigations, in discussion with Infectious Diseases and Rheumatology
- General approach at RCH:
    - **PIMS-TS KD**:
      IVIG 2 g/kg (max 100 g), consider oral prednisolone 2 mg/kg/day (max 60 mg)
    - **PIMS-TS shock**:
      IVIG 2 g/kg (max 100 g), pulse IV methylprednisolone 10 mg/kg/day (max 1 g)
    - **PIMS-TS undefined**:
      consider IVIG, consider oral prednisolone at doses as above.

Note that IVIG is a considerable oncotic load and may precipitate cardiac failure if there is myocardial dysfunction. Consider administering more slowly.

Thromboprophylaxis

- All children should receive low-dose aspirin 3-5 mg/kg oral as a daily dose
- Low-molecular weight heparin (LMWH) may also be indicated, after consultation with the Haematology team

Ongoing Monitoring and Management

- Close clinical observation for recurrence of fevers and signs of ongoing inflammation (e.g., conjunctival injection)
- Regular observations including blood pressure
- Daily weights

If there are signs of ongoing inflammation after initial treatment (fever, rising or persistently elevated inflammatory markers), then further treatment is indicated but should be pursued with consultation by the ID and Rheumatology Teams. Treatment options include a further dose of IVIG, steroid therapy or biologic agents (anakinra, tocilizumab, infliximab).

The risk of coronary artery dilatation/aneurysms in PIMS-TS is 15-25%. Echocardiography is indicated at diagnosis and at 4-6 week follow-up; additional echocardiography as indicated by clinical course in discussion with Cardiology.

Coronavirus (COVID-19)

Children with confirmed or suspected coronavirus (COVID-19) who do not require respiratory or hydration support but are at risk of deterioration can be admitted to HITH for monitoring. As with all HITH admissions, this needs a safe home environment and consent. External referrals are accepted.

HITH (Wallaby) admission criteria and referral

HITH not appropriate

MORE SEVERE ILLNESS (CPG/Taskforce definition)

- Oxygen requirement per clinical judgement
- Persistent tachypnoea
- Requiring NG/IV fluids
- PIMS-TS or similar inflammatory features

→ Admit under appropriate team

MILD ILLNESS AND LOW RISK OR ASYMPTOMATIC

- Mild usually managed by parents +/- GP

→ Refer back to GP

HITH possible

- ASYMPTOMATIC with high-risk co-morbidities (*chronic respiratory/neurodisability/extreme obesity/immunocompromise/cyanotic heart dis) or neonate – most can be GP, case-dependent
- MILD ILLNESS and 1-3 months old
- Support for children out of usual home care
- Social complexity is not an exclusion

HITH appropriate

MODERATELY UNWELL (HITH-specific definition)

- Mild to moderate work of breathing but maintaining oxygen sats >92% in air
- <2/3 usual intake but no NG/IV fluid needed
- Transition to home after inpatient admission

MILDLY UNWELL BUT HIGHER RISK

- Mild symptoms with high-risk co-morbidities*
- Neonates (if febrile, other causes excluded)

→ **Internal:** Contact HITH fellow in hours on 52784 or consultant on call for HITH after hours via switch. Complete EMR HITH referral

External: For referral by clinicians call 93454770.

If accepted, complete referral form at link below

- Referrals are accepted from clinicians in RCH ED/wards/outpatients, external hospitals (including ED), GP, community health, public health, maternal child health nurses, adult HITH colleagues

Prior to family leaving please ensure:

- HITH AUM has obtained consent, current contact information, name and contact details of an alternate person and plan if parent(s) are admitted to hospital
- HITH COVID-19 handout given to family
- Family and referring team are aware that reviews are via telehealth at a specified time. Face-to-face reviews will occur only if clinically indicated. This includes the admission process.
- Complete EMR or external referral form https://www.rch.org.au/wallaby/COVID-19_resources/

Penelope Bryant, Suzanne Boyce, Kate Simpson, Joanna Lawrence & RCH HITH team Updated Nov 2021

HITH protocol – nursing and medical

Daily care requirements

Moderately unwell

Daily medical telehealth review +/- nursing telehealth review in the afternoon

Higher risk, mild symptoms

Daily nursing telehealth review – escalation as required

Telehealth review includes:

- respiratory assessment – work of breathing, activity level, respiratory rate, colour
- hydration assessment – oral intake, wet nappies, activity level

Any concerns will lead to a home visit (staff to wear personal protective equipment (PPE)) or presentation to hospital with parents or via ambulance depending on acuity.

HITH team available 24/7 for family to escalate their concerns – phone calls to come to HITH AUM in hours, ED AUM after hours and escalate to HITH consultant on call as required.

Red flags for escalation

- Inadequate oral intake (< 3 wet nappies in 24 hours, <2/3 oral intake, clinical signs of dehydration) – transfer back to hospital (see below)
- Respiratory deterioration (SaO2 <94%, apnoea, colour change, change in work of breathing) – transfer back to hospital (see below)
- Chest pain/dizziness/palpitations/fainting/breathless (consider myocarditis) – follow RCH CPG
- Fever >5 days, lymphadenopathy, rash (consider PIMS-TS) – transfer back to hospital
- Parental anxiety – increase daily support/telehealth reviews/home visits

Readmission

If clinically appropriate and a ward bed is available, Wallaby will liaise with General Medicine (or most appropriate team) and the bed manager to arrange direct admission to the ward.

If direct admission is not possible or urgent clinical review needed, they will be asked to present to ED. Wallaby will notify the ED admitting officer and General Medicine if this occurs.

Personal protective equipment (PPE)

Airborne precaution PPE prior to entering the home (N95 mask, eye protection, gown, gloves)

Advise only one carer to be in the room during the visit; remind them of physical distancing 1.5 m, no unwell family members in the room

At the end of the visit, once outside, remove PPE into a disposal bag and leave for family to discard. Complete hand hygiene prior to returning to car.

Discharge plan

Discharge when clinical condition improving – patients may deteriorate around 5 days.

If high risk group and mild symptoms, can discharge after 7 days.

Family must continue isolation until advised otherwise by Dept of Health.

Penelope Bryant, Suzanne Boyce, Kate Simpson, Joanna Lawrence & RCH HITH team Updated Nov 2021

Process for prescribing Paxlovid at RCH

Treatment criteria and exclusion criteria are available via the RCH Clinical Management Guidelines Package (available via CPG) or https://rch0365it.sharepoint.com/:u:/s/DPTPharmacy/ERANUxO3YpxMurtQcMfXmxsBePevGr-02BrxuQEn0d4Oxw?e=Z8ov42

Paxlovid is currently not TGA registered for paediatric use, however has emergency TGA approval for its use in patients >12 years of age and >40kg. As a result, consent from the patient (if age appropriate) or the legal guardian is required prior to therapy initiation.

Please click here for the Paxlovid consumer medication information (CMI) handout.

Please click here for the product information for Paxlovid (for clinicians only).

Process:

1) Treating team discusses patient with Infectious Diseases (ID) fellow. On weekends/public holidays, discuss with ID consultant. ID team confirms patient meets treatment criteria and does not meet exclusion criteria.

2) Treating team then discusses with pharmacist and provides telephone number / contact for patient's carer to pharmacist. The pharmacist conducts a medication interview with the patient's carer. The pharmacist assists treating team with information regarding drug interactions and advice re drug alterations that may be necessary.

   During business hours (Mon-Fri): Non-oncology patient: Medicines Information Pharmacist x55208, Oncology patient: oncology pharmacist x56290. After hours (weekends/PHol): on-call pharmacist/oncology on-call pharmacist as appropriate

   Quick tip for RCH patients with complete medication history in the system: create documentation encounter and enter the Paxlovid order in, does a BPA pop up? No – likely no interactions, Yellow – consult with pharmacist, Red – probably excluded due to interactions (still consult with pharmacist)

3) Treating team prescribes medication in EMR. For outpatients, this will be via a prescription sent to RCH Pharmacy. For inpatients, Paxlovid can also be ordered using the inpatient Orders activity.
4) Medication is collected for patient. This may be (in order of preference):

- Non-household contact picks up medication and drops to house
- Household contact arranges to meet treating team outside RCH to take the medication. Household contact must wear a mask. Staff member should wear an N95 and goggles
- Patient's family organises taxi/uber collection
- Medication is delivered to patient via HITH (where patient meets criteria for admission to HITH)
- Medication is couriered to patient (requires Head of Department approval)

5) Treating team has responsibility for follow up of patient – this may be through a HITH admission.

Non-RCH patients:

Paxlovid can be supplied to applicable patients (>12 years of age and >40kg) outside of RCH **ONLY** if the RCH algorithm is followed. Non-RCH clinicians can access the algorithm and medication guideline via the CPG page

RCH ID physicians can give advice to outside clinicians on appropriateness of Paxlovid therapy in adolescent patients, however responsibility of prescribing rests with the outside treating clinician. Medication review and supply can occur via a pharmacy at a hospital more convenient to the patient. Most major regional hospitals will have NMS access to Paxlovid therapy.

If RCH is the most convenient hospital for the patient, then a medical record will need to be created. This can be arranged by contacting HIS: in hours call x56174, out of hours call x56108.

The non-RCH treating clinician has responsibility for follow up of the patient.