Severe Respiratory COVID-19 Wales Pathway
for Children and Young People (CYP) from 0 to 18 years

Noah's Ark Children's Hospital for Wales Ysbyty Plant Cymru

Fever and respiratory symptoms are common in CYP and **NORMAL** algorithms continue to apply!
Mild or moderate COVID does not routinely need investigations or admission.
Severe Respiratory COVID is rare and requires early involvement of consultant(s) & Paediatric COVID MDT.

Acute Severe or Critical CV-19[1]

COVID-19 PCR positive throat swab or suspected (e.g. contact Hx) plus any of the following:
- Oxygen saturation <90% (or deteriorating) in room air (inc.exertional hypoxia)
- Needing respiratory or cardiovascular support

As a minimum do:
***Blood tests*:** FBC, ferritin, U/E, bone, LFT, CRP, Pro-calcitonin, clotting, fibrinogen, di-dimers, troponin, LDH, blood gas, lactate, VITAMIN D and PTH
Blood culture, COVID spike protein antibody and VZV IgG and serum save to virology.
***Throat swabs*:** for full viral respiratory screen and bacterial culture (red and black)
And: CXR, ECG and early ECHO if cardiovascular instability.

Standard of Care and Recovery Trial medication may both be indicated so discuss early with Paediatric COVID MDT (consultant to consultant)

Standard of Care (SOC) [2,3,4,5]

0-24 hrs

Normal Supportive Care as required. **For dosing, prescribing and administration details see Appendix below**

Steroids
Give if ≥ 5 yrs: Dexamethasone oral/NG/IV 150mcg/kg od, max 6 mg) for 10 days (or till discharge if sooner)
Discuss with MDT if under 5 yrs (and sick)

Remdesivir
>12 years AND > 40 kgs consider Remdesivir IV (within first 10 days of illness)
Compassionate use for (sick) younger children only after agreement with MDT

Ronapreve
- Age 12-16 years AND immunosuppressed AND covid PCR positive but ANTIBODY negative

Antibiotics (as per Paediatric Micro guide for severe CAP, unless clearly hospital acquired))
- If < 3months treat as community acquired sepsis
- Over 3 months: Co-amoxiclav IV +/- Azithromycin PO (or Clarithromycin IV)

Tociluzimab (as per Paeds MDT discussion +/- adult physicians)
This is standard of care in adults not responding to Dexamethasone and may be appropriate in certain CYP
Given within first 72 hours or if escalating care despite steroids. Exclude bacterial infection.

VTE-prophylaxis (as per Paeds MDT and meds document)
- COVID is pro-thrombotic, weigh up risk of thrombosis vs Enoxiparin (bleeding)
- Over 12 years also to wear stockings until discharge

Recovery Trial[6]
0-24 hrs

Criteria: FiO2 > 40% to maintain sats 87-97%
or (if ventilated) Oxygenation index: 4 ≤ 16 / Oxygenation saturation index: 5 ≤ 12.3

Age 2-18 years
- Baricitinib (oral or NG) versus SOC

Monitor closely, daily MDT discussion
- Clinical picture can morph into PIMS-TS like hyper-inflammation (typically 2nd week – follow CRP trend)
- Consider PE with sudden change in FiO2, Resp or CVS status (do urgent CT-PA +/- ECHO, treat pending results)
- Consider transfer via WATCh as needed (usual criteria apply)

Discharge

Remember to instigate recent NICE guidance on Vitamin D supplementation
Steroid card and advice if received ≥ 7 days
Advise on pacing/graded exercise and review at 6 weeks (as minimum, pending national guidance)

On behalf of Paediatric COVID MDT, Siske Struik, Consultant Paediatrician UHW November 2021, next review June 2022 or with trial amendments

Noah's Ark
Children's Hospital for Wales
Ysbyty Plant Cymru

Acute Severe Respiratory COVID-19 Wales Pathway

for Children and Young People (CYP) from to 18 years

Key points

Clinical points

- Fever and respiratory symptoms are common in CYP and NORMAL ALGORITHMS for assessment and management continue to apply and must be followed irrespective of the COVID-19 pandemic.
- Mild or moderate paediatric COVID-19 does not routinely need investigations or admission.
- Severe COVID-19 is rare, but can occur, particularly in older children with risk-factors (e.g. obesity)
- **Oxygen requirement** in Covid PCR + children with no other cause (e.g. no RSV) is concerning and should trigger this pathway.
- Acute severe COVID-19 can rarely morph into a hyper-inflammatory PIMS-TS like picture

COVID-19 specific treatments (depends or age and clinical status)

Following learning from the 1st and 2nd wave, several drugs are now established standard of care (SOC). Further drugs are under study. We need to learn ASAP how to optimally treat children and therefore all Paediatric Units are strongly encouraged to recruit eligible patients into research.

Recovery trial – instructions (www.recoverytrial.net)

Decision to enrol requires Paediatric COVID MDT discussion
Consenting and randomisation are done by bedside clinician at local hospital

How to contact Paediatric COVID MDT (same as PIMS-TS)

Core MDT: Paediatric ID, PCCU, Respiratory, with Cardiology and other specialties as needed

Consultant to Consultant (ideally) via UHW Switch (02920747747):

Ask for Paeds ID consultant (Mon-Fri 9-17 hrs). Note there is no formal hours of hours cover – discuss with UHW Gen Paeds Consultant on call who can sign post to JE/SS or St Mary's Hospital if needed)

Local support from Adult services

Especially for older children your local adult colleagues might be able to provide very valuable on site review/advice, as they are far more familiar with acute Severe COVID than most Paediatricians

Location of care

Determined by support needs (usual criteria apply)

How to transfer to UHW PCCU

Contact WATCh retrieval service 0300 0300 789 (usual arrangements apply).

Surveillance and studies we participate in

BPSU, RECOVERY, ISARIC, BATS and p-Sep

References

1. https://www.rcpch.ac.uk/resources/covid-19-guidance-management-children-admitted-hospital
2. https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing- covid19-pdf-661420771099
3. https://covid-19hospitalguideline.wales.nhs.uk/
4. cBNF and Paediatric Microguide (https://viewer.microguide.global/CAVUHB/PAED)
5. All Wales Therapeutics and Toxicology Centrehttps://www.awttc.org/coronavirus-covid-19-therapeutic-advice/covid-19-therapies-alerts-and -advice
6. *Kanthagnany et al Education and Practice EP.BMJ.com June 2021vol 106 issue 3*

Guideline for treatment of Severe COVID-19 in Children and Young People (CYP) 0-18 years

Introduction

This document outlines the pharmacological treatment options for the management of suspected and confirmed severe COVID-19 in CYP.
It complements and supports the Wales pathway for Severe COVID-19 in CYP (April 2021), which includes treatments that are now standard of care, as well as treatments currently only available as part of the Recover Trial.

Of note, this is separate and different from the Wales pathway and pharmacological treatment for PIMS-TS

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Accountable Executive or Clinical Board Director	Dr Clare Rowntree
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1	June 2021	October 2021	June 2021
2	TBA	June 2022	November 2021

For information including definition, clinical management, monitoring and the general principles to treatment, refer to the Wales pathway for Severe Respiratory COVID in Children and Young People (above) and it's reference documents (also listed in Appendix)

TREATMENT

The following treatments are changing rapidly
Please ensure you are using the most up to date version of this guidance.

- Treatment must only be initiated once the MDT has been consulted.
- Consideration for enrolment into RECOVERY trial must be considered for all patients with suspected severe COVID-19
- Patients enrolled in the RECOVERY trial are advised to follow the doses as outlined in the trial document.

1. Corticosteroids (always consider PPI cover)

Dexamethasone

>5 years: PO/IV 150 micrograms/kg (as base) once a day for 10 days (or until discharge from hospital, whichever is first). Maximum dose = 6mg

Dexamethasone can also be considered in children aged between 44 weeks gestational age and 5 years, please discussion with the Paediatric COVID MDT (dose as above).

Hydrocortisone

This can be considered for neonates/infants with a corrected gestational age of ≤44 weeks with COVID-19 pneumonia, please discuss with MDT.
Intravenous: 0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days

Lansoprazole dosing schedule

Body weight	Dose	Notes
>30kg	15-30mg daily in the morning	
15-30kg	15mg daily in the morning	
7.5-15kg	7.5mg daily in the morning	Use half 15mg FasTab
2.5-7.5kg	3.75mg daily in the morning	Use quarter of 15mg FasTab
<2.5kg	1mg/kg daily in the morning	

Administration – See "Lansoprazole in children - C&V Guideline for administration" located on INFORM under lansoprazole

2. Remdesevir (always monitor ALT and Creatinine Clearance)

As per discussion with the Paediatric COVID MDT and in accordance to local adult policy and availability.

Licensed use for Adults, and adolescents ≥ 12 years of age and ≥ 40 kg
Dose: 200mg OD on day 1, then 100mg OD from day 2 for up to 4 further days

Remdesevir should be ordered via the ward pharmacist (for out of hours ring the on-call pharmacist via switchboard)

Compassionate use for children under 12 yrs, and/or weight 3.5 to 40 kg
Dose: 5 mg/kg on Day 1 followed by 2.5 mg/kg OD from day 2 for up to 4 further days
https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fact-sheet-for-hcps.pdf?la=en&hash=D4229149DCD2FF6B7E83F4062C4601BB

Consultant to apply for compassionate use via https://rdvcu.gilead.com/.
Gilead handle requests on a 24-hour basis. Once approval of funding is received, forward this to ward pharmacist (for out of hours ring the on-call pharmacist via switchboard)
to enable delivery to the ward (from Gilead, not hospital stock).

Duration
Treatment should be reviewed daily:
- continued for up to max 5 days (including loading dose)
- consider stopping Remdesivir if:
  - The patient clinically improves and no longer requires supplemental oxygen 72 hours after commencement of treatment; or
  - The patient continues to deteriorate despite 48 hours of sustained mechanical ventilation

Exclusion and Further Stopping criteria
- Patients who present to hospital more than 10 days after symptom onset.
- ALT ≥ 5 times the upper limit of normal (Remdesivir may be restarted when ALT is < 5 times the upper limit of normal)
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR)
- CrCl <30 mL/min (use Schwartz formula for under 18s)
  Schwartz formula
  Child >1 year: 40 x height (cm)/Serum Cr (micromol/L)

3. **Ronapreve** (casirivimab and imdevimab)

As per discussion with the Paediatric COVID MDT and in accordance to local adult policy and availability.

For children and young people who full-fill all of the criteria below:

- 12 years and older
- weighing ≥ 40 kg
- deemed immunocompromised
- SARS-COV-2 PCR positive
- Covid spike antibody negative

If eligible, this should be given as soon as possible after the PCR positive result

Dosing (same as adults): 600mg Casirivimab and 600mg Imdevimab administered together as a single infusion intravenously (or subcutaneously).

For administration and further details:

Summary of Product Characteristics for Ronapreve - GOV.UK (www.gov.uk)

4. Antibiotics (follow and see Paediatric Microguide CAV for COVID-19)

In brief:

If infant under 3 months of age: treat as community acquired sepsis, unless hospital acquired.

SEPSIS
First Choice
<3months: Cefotaxime IV **plus Amoxicillin (50mg/kg)** IV
Second Choice / Alternative agents
Discuss with microbiology
Duration
Treatment duration: Minimum 7 days. To be discussed with microbiology and decided according to possible cause of illness.

*Please, **also consider HSV infection** in the differential diagnosis of infants < 6 weeks of age; if they have vescicular rash, abnormal clotting and LFTs.*
If considered, send eye, rectal and throat swabs for HSV (red topped) to virology and start **Aciclovir** IV.

If age 3 months and over: treat as severe community acquired pneumonia (CAP), unless hospital acquired.

First choice

>3 months: SEVERE: **Co-amoxiclav** IV
plus/minus
ClarithromycinIV or **Azithromycin**PO

Second choice/Alternative agents

Penicillin allergy-SEVERE: **Clarithromycin**IV or **Azithromycin**PO or consult with Microbiology for further advice

Duration

SEVERE: for 7-10 days

5. Tocilizumab (IL-6R inhibitor) – as Rescue therapy

Via ward pharmacist or from emergency cupboard via site practitioner out of hours.

- Tocilizumab is licenced over 18 years of age as part of standard of care in adults of with Severe Respiratory COVID who are not responding to Dexamethasone.

- It has not been trialled in CYP for severe respiratory disease, but clinical situations may arise where RESCUE with Tocilizumab is deemed more appropriate than randomisation to Baricitinib versus standard of care, for which equipoise to the latter would be required. This decision requires discussion with the wider Paediatric COVID MDT and where practicable also with adult counterparts.

- Of note, Baricitinib and Tocilizumab should not be given together.

Please note that co-existing bacterial infection may be worsened by IL-6 blockade (review pro-calcitonin). Detailed guidance around indications, contra-indications and dosage can be found on the **Adult Microguide COVID page**. In brief:

Intravenous
Age >1 year
<30kg 12mg/kg (a second dose may be given at ≥ 12 and ≥ 24 hours later per MDT discussion)
≥ 30 kg 8mg/kg (max 800mg) (a second dose may be given at ≥ 12 and ≥ 24 hours later under MDT discussion)

Administration (Via Syringe pump) **to be given over 1 hour**
CHILD less than 30kg:
Calculate the volume of tocilizumab concentrate required for the prescribed dose.
Remove the equivalent volume from a 50mL sodium chloride 0.9% infusion bag and discard.
Withdraw the dose from the vial(s) and add to the infusion bag.
Mix by gently inverting the infusion bag to avoid foaming.

CHILD 30kg and over:
Calculate the volume of tocilizumab concentrate required for the prescribed dose.
Remove the equivalent volume from a 100mL sodium chloride 0.9% infusion bag and discard.
Withdraw the dose from the vial(s) and add to the infusion bag.
Mix by gently inverting the infusion bag to avoid foaming.

Adverse effects: Hypersensitivity reactions including anaphylaxis, flushing, fever, chills, rash, pruritus, urticaria, headache, hypertension.
Monitor: Pulse, blood pressure, temperature & respiration rate for any signs of hypersensitivity reaction. Baseline observations should be measured after 15 minutes, then every 30 minutes until 1 hour post infusion.

6. VTE Prophylaxis for suspected or confirmed severe respiratory COVID-19 in CYP (remember Creatinine Clearance)

All children over 12 years of age should wear compression stockings until discharge home.

Prophylactic enoxaparin

The decision whether to give Enoxaparin is reached via discussion with the Paediatric COVID MDT.

Guiding principles:

Adults with COVID driven inflammation are at high risk of thrombosis and are given prophylaxis. The picture in children is not clear cut, and requires individualised consideration of risks of thrombosis versus the risks of enoxaparin (bleeding). Note that enhanced prophylactic dosing is no longer recommended.

For young people over the age 16 years, in principle you should follow adult guidelines on intranet

Indications to consider Enoxaparin

- older children/teenagers
- excess weight
- significant immobilisation
- significant inflammation (fever, inflammatory markers)
- central line
- pre-existing other pro-thrombotic conditions

Contraindications to Enoxaparin

Active bleeding/high risk of bleeding, lumbar puncture or epidural anaesthesia within the past 6h or due in the next 24h, severe hypertension over the 99th centile, thrombocytopenia: platelet count < 50 x 109 /L, acute bacterial endocarditis

For invasive procedures (LP or operations) must be >24hours off last dose before needle/knife to skin.

Prophylactic dose Enoxiparin as per cBNF

Children under the age of 1 month
750micrograms/kg twice daily (Round to the nearest mg for ease of administration)

Children over the age of 1 month – 16 years
500micrograms/kg twice daily. MAX: 40mg per day

If 101-150 kg: Enoxiparin 40 mg bd
If >150 kg: Enoxiparin 60 mg bd

Please note that with renal impairment eGFR should be calculated (below) and if under 30ml/min, dose adjustment is required. Discuss with hematology. As a guide, start with 50% of normal dose, and check levels 2-4 hrs after 3rd dose, aiming for anti Xa levels of 0.1 iu/dl.

Age	**Estimated eGFR equation** (mL/minute/ 1.73 m2)
Child over 1 year:	40 x height (cm)/serum creatinine (micromol/ litre)

Child between 1 month and 1 year:	35 x height (cm)/serum creatinine (micromol/ litre)
Neonate	30 x height (cm)/serum creatinine (micromol/ litre)

Treatment dose Enoxaparin as per cBNF

Indications: suspected pulmonary embolism, confirmed thromboembolism, or significant coronary artery aneurysm

If platelets <50 x10^9/L then discuss with paediatric haematology. As a guide: in first month of treatment support platelets with transfusion and keep above 50. Once out of first month then stop when platelets fall to < 50

For invasive procedures (LP or operations) must be >24hours off last dose before needle/knife to skin.

Refer to Paediatric Thrombosis and Anticoagulation Guidelines (2014) or Cardiology clinical guidelines (2019) for information on Dosage, Monitoring and Factor Xa Levels. Both can be found on the "Paediatric Cardiology" section of intranet

7. **Baricitinib** (Think pregnancy test and always monitor neutrophils and eGFR)

Age 2-18 years as part of Recovery Trial

Route: oral or NG
Frequency: Once daily for 10 days or until discharge, whichever is sooner

Dosing table based on age and eGFR:

eGFR (ml/min/1.73m2)	2 to < 9 yr	≥ 9 yr
≥60	2mg	4mg
≥30 - <60	2mg alternate days	2mg
≥15 - <30	Excluded	2mg alternate days

Contraindications: Neutrophil count <0.5 x109/L, and/or on renal replacement therapy

Prescribe on Trial form (Appendix 2) as well as drug chart and contact ward pharmacist (clinical trials are only available during pharmacy opening hours)

References:

1. *Cardiff and Vale UHB (2015) 'Lansoprazole in children - C&V Guideline for administration',version 1, pp. 1-2 (Accessed: 09/05/2020).*
2. *BPAIIG (2020) Position Statement: Management of novel coronavirus (SARS-CoV-2) infection in paediatric patients in the UK and Ireland: Version 1.2, Available at: https://www.bpaiig.org/sites/default/files/National_paediatric_COVID19%20treatment%20v1.2_0.pdf (Accessed: 09/05/2020)..*
3. *Paediatric Formulary Committee. BNF for Children (online) London: BMJ Group, Pharmaceutical Press, and RCPCH Publications <http://www.medicinescomplete.com> [Accessed on 09/05/2020]*
4. *Welsh Medicines Information Centre (2020) 'How should medicines be dosed in children who are obese? ', Medicines q&a,version 1.2, pp.3. Available at: https://www.sps.nhs.uk/articles/how-should-medicines-be-dosed-in-children-who-are-obese/*

5. *Royal College of Paediatrics and Child Health (2021) COVID-19 - guidance for management of children admitted to hospital. Available at:* **https://www.rcpch.ac.uk/resources/covid-19-guidance-management-children-admitted-hospital** *(Accessed 07/01/2021)*
6. https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing- covid19-pdf-66142077109189
7. https://covid-19hospitalguideline.wales.nhs.uk/
8. Kanthagnany et al Education and Practice, EP.bmj.com June 2021
9. Paediatric Microguide (https://viewer.microguide.global/CAVUHB/PAED)
10. Adult Microguide (https://viewer.microguide.global/CAVUHB/ADULT)
11. All Wales Therapeutics and Toxicology Centre

https://www.awttc.org/coronavirus-covid-19-therapeutic-advice/covid-19-therapies-alerts-and-advice

CLINICAL TRIAL PRESCRIPTION

RANDOMISED EVALUATION OF COVID – 19 THERAPY (RECOVERY)

Paediatric Tocilizumab Prescription

Investigator: Prof Chris Fegan

Lead for Paediatrics: Dr Julian Forton

Patient details *(addressograph)*

Weight……kg

Patient Trial Number:…….

Ward……

Please dispense the following to the above patient:

Tocilizumab IV ……..mg

Dose determined by body weight:

Weight	Dose
Under 1 year of age	Excluded
< 30kg	12mg/kg
≥ 30 kg	8mg/kg (max dose 800mg)

- Based on vial size availability, doses can be rounded in accordance to the Roche dosing guide in order to minimise wastage and to allow doses to be measured accurately. Refer to page 7: https://www.medicines.org.uk/emc/rmm/1393/Document

Prescriber's Signature.....Date.....

Prescriber's Name……..Bleep/Ext.....

PHARMACY USE ONLY

Clinical Check**.....*****Date*****.....**

Dispensed by**.....*****Date*****.....**

Checked by**..... *****Date*****.....**

Please initial once complete:

Prescription signed and dated	Disp	Checker .....
Site Signature log signed and dated	Disp.....	Checker.....
Accountability Logs signed/dated	Disp	Checker.....

CLINICAL TRIAL PRESCRIPTION

RANDOMISED EVALUATION OF COVID – 19 THERAPY (RECOVERY)

Baricitinib Prescription

Investigator: Dr Matt Wise

Patient details (addressograph) eGFR……ml/min

Patient Trial Number:……. Ward……

Please dispense the following to the above patient

Dosage Instructions	Tick dose required
Baricitinib 4 mg once a day for 10 days	
Baricitinib 2 mg once a day for 10 days	
Baricitinib 2mg on alternate days for 10 days	

Prescriber's Signature.....Date.....

Prescriber's Name……..Bleep/Ext.....

PHARMACY USE ONLY

***Clinical Check*.....*Date*.....**

***Dispensed by*.....*Date*.....**

***Checked by*..... *Date*.....**

Please initial once complete:

Prescription signed and dated	Disp	Checker .....
Site Signature log signed and dated	Disp.....	Checker.....
Accountability Logs signed/dated	Disp	Checker.....