BPAIIG British Paediatric Allergy Immunity & Infection Group

Position Statement: Management of novel coronavirus (SARS-CoV-2) infection in paediatric patients in the UK and Ireland

PLEASE NOTE: THIS GUIDANCE IS SUBJECT TO CHANGE WITH EMERGING EVIDENCE

1. Introduction

This guidance covers possible antiviral management of paediatric patients with suspected or confirmed novel coronavirus infection (SARS-CoV-2) in the UK and Ireland. Whilst there are no antivirals licensed for use in this indication, data from SARS-CoV-1, MERS-CoV and *in vitro*, *in vivo* and limited clinical studies suggests some benefit may be obtained from antiviral therapy [1, 2].

Although SARS-CoV-2 appears to cause milder disease in children compared to adults, there is still little known about the pathophysiology and clinical spectrum of the disease in this patient group. No comorbidity has been shown to be a risk factor for severe diseases in children as yet, although data are accumulating. Patients, regardless of comorbidity, with confirmed or suspected COVID-19 and signs of progressive respiratory deterioration, especially hypoxia, may be considered for antiviral or immunomodulatory medication.

Our recommendation is that as far as possible, all patients in the UK should only receive anti-viral or immunomodulatory treatments for COVID-19 within a treatment trial.

At the time of writing, there were no treatment trials that allowed enrolment of children, however this is likely to change. Please check for updated guidance.

Patients should be considered for compassionate use of antiviral treatments on a case by case basis in discussion with the recommended specialists outlined below.

There are extremely limited supplies of all COVID-19 medications nationally, this should be taken into account for all treatment decisions.
This document was developed by members of the paediatric infection community (Microbiology/Infection Pharmacy/Infectious Diseases), rheumatology community, immunology community, BMT community and intensive care community nationally to provide guidance to frontline clinicians caring for patients with COVID-19. It is based on the GOSH and Imperial College Healthcare NHS Trust (ICHT) treatment guidance, thank you to all teams for their input.

The document covers potential off-label and/or experimental treatment use of medications, and aims to provide a framework for case-by-case discussion with specialists who can provide additional advice. It also suggests appropriate laboratory investigations.
The document does not cover infection control and personal protective equipment (PPE). Please refer to national guidelines.

This is a living document that will be updated in real time as more data emerge. It appears that pharmacological antiviral treatment is most effective if initiated quickly upon clinical presentation, prior to clinical deterioration, however treatment of mild cases is not recommended and confirmatory evidence is pending.

2. General Key Considerations

1. **Treating team to contact paediatric ID team, PICU and/or retrieval service for severely unwell children with suspected or confirmed COVID-19 – If rapidly deteriorating patient, involve PICU early**
2. **Send appropriate investigations** as described in diagnostic tests section
3. **Consider ceilings of care early in all children with underlying disease**
4. **Consider carefully the use of:**
   - **Corticosteroids**
   - **Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs)**
   - **Nebulisers (use inhalers with an aerochamber preferentially)**
5. **We recommend a nose and throat swab in lieu of a nasopharyngeal aspirate to minimise aerosolisation**
6. **Only initiate NIV/HFNCO in an appropriate setting (ideally negative pressure room, or side room if negative pressure room not available)**

7. **Most COVID-19 patients do not require antibiotics.** However, if there is a strong suspicion of bacterial infection, antibiotics should be prescribed as per local antimicrobial guidelines. Contact the paediatric ID/micro team early to provide advice on challenging cases.

3. Additional diagnostic tests for severely unwell children with suspected/confirmed COVID19

The majority of children are expected to have asymptomatic or mild disease only. No additional blood tests are required for children with mild-moderate disease requiring only supportive care, beyond those required to exclude alternative diagnoses. Given the relatively mild symptomatology of the majority of children with COVID19, it is vital that alternative diagnoses are considered in children presenting as unwell, following the same investigation and management practice and pathways in place prior to the outbreak.

Children presenting or deteriorating with severe features consistent with ARDS should have the following investigations (listed in Table below). Samples (respiratory and blood) should be sent for virology testing prior to initiating any antiviral or immunomodulatory treatment and all patients should be discussed with a paediatric infectious diseases team.

Initial diagnostic tests	
Haematology / Biochemistry	FBC, U+E, LFT, CRP, Troponin, Ferritin, LDH, coagulation panel including D-Dimer, triglycerides *if considering immunomodulatory treatment send IL6 and soluble CD25
Microbiology	Blood cultures, Urine MC&S, viral respiratory panel *HIV testing should be done in all children in whom treatment with lopinavir/ritonavir is being considered, but pending results should not delay treatment.
Radiology	Chest x-ray
Other	Serum save, research bloods if appropriate in your setting In children <2 years of age consider lymphocyte subsets to exclude SCID (severe or critical illness only)
Suggested ongoing monitoring tests (if deteriorating patient)	
Haematology / Biochemistry	FBC, U+E, LFT, CRP, Ferritin

4. Treatment criteria

There is currently limited evidence of efficacy of antiviral and immunomodulatory therapy for COVID19 in adults, and no evidence in children. The decision to start treatment should be made carefully on a case by case basis. We recommend discussion within already established internal review pathways, but also suggest discussion with an external Paediatric Infectious Disease Specialist prior to starting antiviral therapy and/or a clinician with experience in the use of immunomodulatory therapy if these are being considered (Immunology, Haematology, Bone Marrow Transplant, Rheumatology). Antiviral treatment is likely to have the most benefit in the first phase of illness. Immunomodulatory therapy may only be indicated if clear evidence of hyperinflammation, or in the second phase of the illness, and evidence is currently extremely limited. Antiviral treatment and immunomodulatory treatment should be restricted for hospital use only and preferably in a clinical trial setting.

Treatment criteria		
Mild to moderate disease No O_2 requirement Mild upper airway infection	All groups	Supportive care
Severe disease Mild - moderate ARDS**: 1) Unventilated requiring FiO2 >40% to maintain saturation 88-97% 2) Ventilation: - Oxygenation index: 4 ≤ 16 - Oxygenation saturation index: 5 ≤ 12.3	All groups Risk group*	Supportive care Treatment with antivirals may be considered in all Treatment with immunomodulatory therapy may be considered (especially in a risk group) if evidence of hyperinflammation (raised CRP, ferritin, IL6, sCD25)
Critical disease Severe ARDS**: - Oxygenation index: ≥16 - Oxygenation saturation index: ≥12.3 Septic shock Altered consciousness Multi-organ failure	All groups	Supportive care Treatment with antivirals may be considered Treatment with immunomodulatory therapy may be considered if evidence of hyperinflammation (raised CRP, ferritin, IL6, sCD25)

* **Risk groups, Appendix A** - Children in risk groups should be seen as at particular risk of clinical deterioration and risk benefit based decisions relating to antiviral or immunomodulatory therapy should take this into account.

** ARDS as defined by the PARD criteria: Pediatric Acute Lung Injury Consensus Conference Group [3]

5. Antiviral therapy

This treatment guidance will be reviewed regularly as the situation develops.

Samples (respiratory and blood) should be sent for virology testing prior to initialising treatment and all patients should be discussed with microbiology/paediatric infectious diseases.

For the agents mentioned below, please contact pharmacy with regard to dosing in neonates or patients with renal impairment. The following has been developed by the University of Liverpool to be used to check the potential for drug interactions: http://www.covid19-druginteractions.org/.

The treatments are not listed in any particular order.

Please note: this document will be regularly updated. It is advisable to save the link rather than the PDF document itself. If you have saved this document, please re-check this link regularly to ensure you have the most up to date version.

For patients in whom treatment with lopinavir/ritonavir (Kaletra) is being considered, an HIV test should be performed to avoid selecting for resistance in an undiagnosed child.

Treatment choice:	Drug:	Route:	Dose:			Duration:	Available drug forms & comments:
			Formulation:	Weight:	Dose:		
EITHER:	Lopinavir-ritonavir (Kaletra)	Oral/ NG	Oral liquid 400/100mg in 5mL [4]	3-5kg	1mL 12 hourly	7 days	**Liquid**: 5ml = LPV/RTV 400/100mg (clear) NB: Fridge (contains 42% ethanol and propylene glycol) - caution in neonates. **Tablets:** 100/25mg and 200/50mg available. **NB**: do not use in neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days
				6-9kg	1.5mL 12 hourly		
				10 - 13kg	2mL 12 hourly		
				14-19kg	2.5mL 12 hourly		
				20 - 24kg	3 mL 12 hourly		
			Tablet [4]	10-13kg	200/50mg morning 100/25mg at night		
				14-24kg	200/50mg 12 hourly		
				25-34kg	300/75mg 12 hourly		
				> 35kg	400/100mg 12 hourly		
	PLUS Ribavirin	Oral/ NG	Oral solution/ tablet/ capsule [5]	10mg/kg (max 900 mg) 12 hourly		7 days	Round tablet/capsule doses to nearest 200mg, can split total daily dose of 20mg/kg into 3 to aid administration. Tablets can be crushed for NG if no oral solution available.
OR:	Chloroquine	Oral/ NG	Oral solution/ tablet [6]	10mg/kg chloroquine base (max 620mg) initial dose, followed by dose of 5mg/kg after 6 hours, then 5mg/kg		3 days ONLY	Chloroquine 250mg (containing 155mg chloroquine base)

				once daily thereafter			tablets; round to nearest half tablet where able. Crush tablets for NG administration
OR:	Hydroxy-chloroquine	Oral/ NG	Oral solution /tablet [7]	6.5 mg/kg 12hourly on day 1 (maximum initial dose = 400 mg), followed by 3.25 mg/kg 12hourly on days 2 - 5 (maximum dose = 200 mg)		5 days	Tablets can be crushed Oral solution (unlicensed special)
OR:	Remdesivir (GS-5734)	IV	100mg or 150mg vials powder/solution for infusion [8]	<40 kg	**5mg/kg loading dose**, then 2.5mg/kg once daily	10 days total including loading dose	Compassionate use from Gilead, see below
				≥40 kg	**200mg loading dose**, then 100mg once daily		

6. Obtaining remdesivir

IMPORTANT: There are currently extremely limited antiviral data for remdesivir that show activity against the SARS-CoV-2. However, we understand the virus is closely related to SARS-CoV and remdesivir is active against SARS-CoV and MERS-CoV both in vitro and in animal models. Remdesivir is not yet licensed or approved anywhere globally. While remdesivir is in development, Gilead is committed to providing the drug where appropriate for compassionate use, whilst managing the balance of potential global demand vs supply.

All suspected or confirmed paediatric cases of COVID19 for whom antiviral or immunodulatory treatment is being considered should be referred to a paediatric infectious diseases consultant and any decision to treat should be approved by local MDT and also be approved by a paediatric infectious diseases consultant from at least 1 additional centre in the UK or Ireland.

7. Immune modulation therapy

Some patients with SARS-CoV-2 infection and ARDS have clinical features / blood parameters which overlap with well recognised hyperinflammatory syndromes, including secondary Haemophagocytic Lymphohistiocytosis (sHLH), sepsis associate Macrophage Activation-Like Syndrome (MALS) and CAR-T cell therapy associated Cytokine Release Syndrome (CRS). Inflammatory pathology appears to more localised within the lung tissue in SARS-CoV-2 infection, and systemic inflammatory markers are generally lower than in these other syndromes.

Raised inflammatory markers (CRP, ferritin, IL6) [9,10] appear to be associated with more severe disease and a worse prognosis. Tocilizumab (a humanised anti-IL6 monoclonal antibody) is an established therapy for CRS following CAR-T cell therapy, and has been used to treat hyperinflammation in SARS-CoV-2 infection with anecdotal success and no significant toxicity [11]. There are ongoing randomised controlled trials of Tocilizumab in SARS-CoV-2 infection in Italy and China. Anakinra is a recombinant antagonist of the human IL1 receptor and is an established therapy in macrophage activation syndrome, sHLH (off-licence) and has demonstrated a survival benefit in patients with MALS. Although both Tocilizumab and Anakinra are generally well tolerated, they both confer an increased risk of infection, so careful assessment of co-infection should be made prior to use, especially as co-infection in the context of SARS-CoV-2 is a risk factor for poor outcome.
As with decisions to use antiviral medication the use of immunomodulatory therapy should be considered on a case by case basis involving broad MDT (including specialists in the use of these agents) and ethics team if necessary. It is also recommended to discuss with at least one specialist external to the treating Trust.

Treatment choice:	Drug:	Route:	Dose:			Duration:	Comments:
			Weight:	Formulation:	Dose:		
	Tocilizumab	IV	<30 kg	20 mg/ml single dose vials. Dilute to 50ml with 0.9% Sodium Chloride	12 mg/kg	If no improvement at 12 hours, repeat with same dose	
		IV	≥30 kg	20 mg/ml single dose vials. Dilute to 100ml with 0.9% Sodium Chloride	8 mg/kg (max dose 800mg)		

Or	Anakinra	SC		100mg in 0.67mL pre-filled syringe	2mg/kg once daily. Increase dose by 2mg/kg per day if unresponsive. Maximum dose 8mg/kg	Stop if no clinical benefit at maximum dose	
		IV	<20 kg	100mg diluted in 0.9% sodium chloride, 24 ml total volume	2mg/kg stat loading dose, followed by a continuous infusion of 0.02ml/kg/hr (2mg/kg/day). Increase by dose by 2mg/kg/day every 12 hours if unresponsive. Maximum dose 12mg/kg/day		Maximum dose in 24 hours 400mg (excluding loading dose) Syringe must be changed every 8 hours.
			>20 kg	100mg diluted in 0.9% sodium chloride, 12 ml total volume	2mg/kg stat loading dose, followed by a continuous infusion of 0.01ml/kg/hr (2mg/kg/day). Increase by dose by 2mg/kg/day every 12 hours if unresponsive. Maximum dose 12mg/kg/day		

8. Clinical Trials for COVID19

There are currently no clinical trials or studies active in the UK for recruitment of paediatric patients, but this is a rapidly changing field.

The following interventional clinical trials and national observational studies are active in the UK for recruitment for hospitalised patients:

a. **RECOVERY trial** (UK study; standard of care versus lopinavir/ritonavir vs. interferon beta-1a vs. dexamethasone vs hydroxychloroquine)
b. **REMAP-CAP** (international critical care study, UK sites; expanded to include COVID-19-specific arms for standard of care versus lopinavir/ritonavir (Kaletra) and standard of care versus interferon-beta-1a, and interleukin-1 receptor antagonist (Anakinra)
c. **ISARIC-CCP** UK Case Record Forms (CRF) are available for the collection of standardised clinical data on suspected or confirmed cases of COVID-19

The following interventional clinical trials and national observational studies are emerging or proposed in the UK:

a. **DISCOVERY trial** (WHO pan-European; standard of care versus standard of care + remdesivir versus standard of care + lopinavir/ritonavir versus standard-of-care + lopinavir/ritonavir + Interferon beta-1a)
b. Proposal to amend the **REALIST trial** (acute respiratory distress syndrome) to include patients with COVID-19 / HLH and use of anakinra or tocilizumab
c. **ACTT** trial (remdesivir versus standard-of-care)

9. References

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Appendix A - Risk Groups

1. Long term respiratory conditions including:

   Chronic lung disease of prematurity with oxygen dependency

   Cystic fibrosis with *significant respiratory problems*

   Childhood Interstitial lung disease

   Severe Asthma

   Respiratory complications of neurodisability

2. Immunocompromise (disease or treatment) including:

   Treatment for malignancy

   Primary immunodeficiency*

   Immunosuppressive medication** including long term (>28 consecutive days) of daily oral or IV steroids (not alternate day low dose steroid or hydrocortisone maintenance)

   Post-transplant patients (solid organ or stem cell)***

   Asplenia (functional or surgical, includes sickle cell disease)

3. Haemodynamically significant and/or Cyanotic heart disease
4. Children <1yrs of age

* Primary immunodeficiency
- Combined immunodeficiency
- CD4 lymphopenia (CD4 count <200 x106/L) in the context of any other immunodeficiency , includes HIV
- Any primary immunodeficiency (requiring treatment with prophylactic antibiotics or immunoglobulin) and taking immunosuppressive medication

** Immunosuppressive medications include: Azathioprine, Leflunomide, methotrexate, Mycophenolate (mycophenolate mofetil or mycophenolic acid), ciclosporin, cyclophosphamide, tacrolimus, sirolimus. It does **NOT** include Hydroxychloroquine or Sulphasalazine either alone or in combination. Biologic/monocolonal includes –

Rituximab within last 12 months; all anti-TNF drugs (etanercept, adalimumab, infliximab, golimumab, certolizumab and biosimilar variants of all of these); Tociluzimab; Abatacept; Belimumab; Anakinra; Seukinumab; Ixekizumab; Ustekinumab; Sarilumumab; canakinumab. Small molecules include all JAK inhibitors – baracitinib, tofacitinib etc

***For post transplant patients, those who are currently:

- less than 1 year following transplant; are still taking immune suppressing drugs; are on immunoglobulin replacement therapy; have significant lung disease; or have ongoing chronic graft versus host disease