CLINICAL MANAGEMENT OF CONFIRMED COVID-19 CASE IN ADULT

A. Clinical Management of Confirmed COVID-19 Case in Adult

Table 1: Clinical Staging of Syndrome Associated with COVID-19

Clinical stage	
1	Asymptomatic
2	Symptomatic, No Pneumonia
3	Symptomatic, Pneumonia
4	Symptomatic, Pneumonia, Requiring supplemental oxygen
5	Critically ill with multi-organ involvement

1. General Care

a. Patients with COVID-19 illness should receive symptomatic treatment such as antipyretics, optimal nutritional support, maintenance of fluid and electrolytes balance.
b. Patients with COVID-19 illness should have close monitoring of vital signs according to clinical staging of illness and monitored for progression of disease. There should be clear mechanism for close follow up and pathway of referral in case of need of escalation of medical care (Table 4).
c. Patients with COVID-19 illness should have regular blood investigations and imaging as recommended in Table 4.
    - Inform laboratory staff before sending specimens according to local COVID-19 pathway.
d. For those who need bronchodilator therapy e.g. Salbutamol; avoid using nebulizer. Instead use MDI with spacer.
e. In patients with COVID-19 who require supplemental oxygen, we suggest a trial of self-proning, if the patient can tolerate it. Patients need to be closely monitored for desaturations during the trial of self-proning.
f. In general, the use of non-invasive ventilation is discouraged when managing patient with COVID-19. However, recent publications suggest that newer High Flow Nasal oxygenation (HFNO) and Non-invasive ventilation (NIV) systems with good interface fitting do not create widespread dispersion of exhaled air.
g. Patients with COVID-19 illness should not be routinely prescribed antibiotics unless suggestive of bacterial illness.

2. Clinical progression of COVID-19

a. Majority of the patients present with mild disease in clinical category 1 to 3.
b. Patients with age $\geq$50 and those with chronic comorbid illnesses have higher risk of developing more severe disease.
c. Clinical deterioration happens in about 10-15 % of cases, with new or worsening respiratory symptoms within 5 to 12 days of the onset of mild symptoms. This deterioration can be due to the following reasons (aetiologies may overlap):
    i. Cytokine Release Syndrome (CRS) which is a systemic

inflammatory response associated with rapidly worsening pneumonia with or without multi-organ involvement.

ii. Viral effect of the disease, typically in the first week of illness or can be prolonged if immunomodulatory drugs were given too early.
iii. Decompensation of underlying comorbid illness.
iv. Complications such as Thromboembolism, Nosocomial pneumonia.

3. Specific Treatment

a. No antiviral treatment for COVID-19 infection is currently approved.
b. The treatment regimen suggested below is likely to change as new evidence emerges. Kindly discuss with ID physician or ID paediatricians for specific treatment.

Table 2: Specific treatment of COVID-19 disease

Category	Treatment
1	No treatment required
2	No treatment required • Close observation of vital signs and oxygen saturation as stated in monitoring guidelines. Look for warning signs at each review.
3	Generally, no treatment required • Close observation of vital signs and oxygen saturation as stated in monitoring guidelines. • Treat with Favipiravir as category 4 if patient has any of the following risk factors: o Age ≥ 50years with co-morbid o ESRF (consult ID physician on the choice of treatment) o In the presence of any warning signs (see below)
Warning Signs that predict deterioration Clinical • Persistent or new onset fever • Persistent symptoms - Lethargy/ anorexia/ cough • Reduced level of consciousness in the absence of alternate explanation such as hypoglycaemia, uraemia etc. • Respiratory compromise o Exertional dyspnoea / desaturation o Respiratory rate more than 25 o SpO2 room air <95%	

Laboratory

- A rising CRP value or a single CRP value of ≥50mg/l*
- Dropping Absolute lymphocyte count (ALC) or a single value < 1
- Neutrophil lymphocyte ratio ≥ 3.13

Radiological

- Features of severe pneumonia, multi- lobular involvement, or rapidly worsening chest X-ray

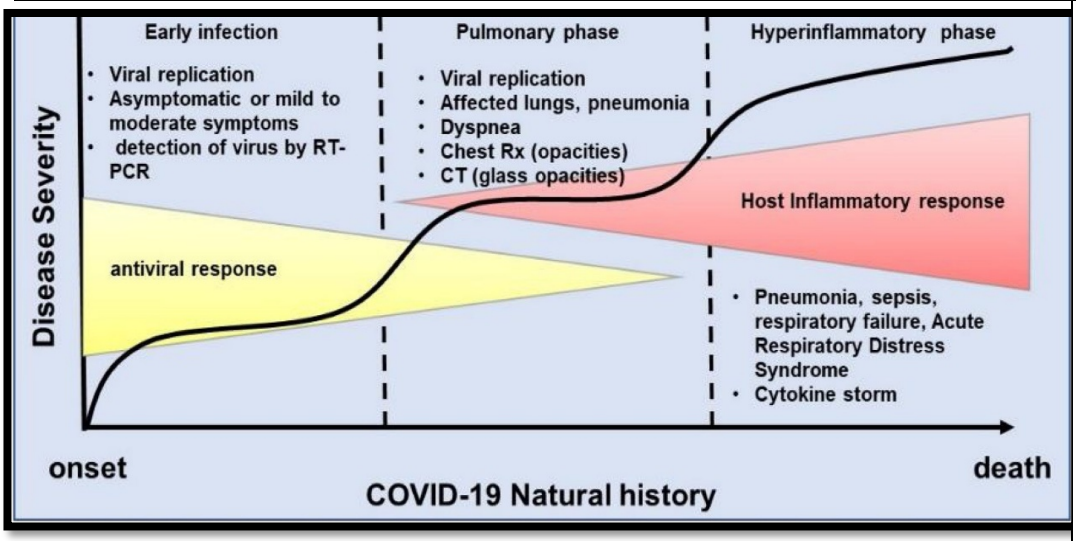
** Patients who are deteriorating clinically and radiologically, especially in the first week of illness, but do not have raised CRP, the cause of deterioration can be due to either uncontrolled viral effect, decompensation of underlying comorbidity, thromboembolism or other concomitant infection rather than due to inflammation.*

4

- **A) Antiviral treatment**

Drug	Dose & Duration	Comments
Favipiravir	1800mg bd for 1 day then 800mg bd 5 days Optimal duration of antiviral treatment is unknown. A study on Remdesivir showed no difference between 5 day and 10 day course of treatment (JAMA. doi:10.1001/jama.2020.16349) Antivirals have not shown to be effective when initiated in hyper inflammatory phase of disease (see figure below). Consider stopping or not initiating the drug in hyperinflammatory	Teratogenic effect: Favipiravir is contraindicated for women of childbearing potential and men whose partner is of childbearing potential. In this group, if Favipiravir is used, they should be advised to use contraception for 7 days after the last dose of Favipiravir Avoid if GFR <30ml/min Consult ID physician for usage in ESRF patients on regular dialysis. Common side effects: • Hyperuricemia • Diarrhoea • Elevated transaminase • Neutropenia

	phase of the disease.	Drug interactions: • Paracetamol – maximum 3gm per day • Theophylline – increases Favipiravir levels • Pyrazinamide – both cause hyperuricemia



Adapted from, https://doi.org/10.1016/j.biopha.2020.110493.

B) Immuno-modulatory treatment

If there is disease progression with evidence of inflammation, consider adding steroids or Tocilizumab

Drugs	Dose & Duration	Comments
Dexamethasone	6mg od oral or IV daily 5-10 days In patients **presenting with severe disease** (requiring high flow mask or ventilation) and high inflammatory markers, consider a higher dose of Dexamethasone, 8-12 mg in 1-2 divided doses (equivalent to 1-2mg/kg/day of methylprednisolone*) Start tapering the	Recommended in all patients needing supplemental oxygen. Steroids are more likely to be useful for hypoxic patients who also show evidence of inflammatory response such as high/raising CRP, LDH, or Ferritin. Consider other causes of hypoxia such as bacterial pneumonia, cardiac failure, fluid overload and

	dose within 3- 5 days or as soon as there is response. In patients **progressing while on the initial dose (6mg od)** along with increasing inflammatory markers, consider doubling the dose of steroids. Start tapering the dose within 3- 5 days or as soon as there is response. In patients progressing while on the initial dose (6mg od) along with increasing inflammatory markers, consider doubling the dose of steroids. Start tapering the dose within 3- 5 days or as soon as there is response.	pulmonary embolism **Duration and tapering dosage.** In mild cases 5- 10 days of steroids is adequate. Steroids can be stopped 48-72 hrs after patient has responded clinically with reducing CRP. In severe cases, to prevent a rebound in hyperinflammation, gradually taper steroids (over 2-3 weeks) guided by the degree of hypoxia and CRP. * Methylprednisolone 1mg equivalent to Dexamethasone 0.2mg.
Methylprednisolone	1-2 mg/kg for 3-5 days and subsequently taper with Dexamethasone as above. In patients presenting with severe disease (high flow mask, ventilation on arrival) Methylprednisolone can be used initially before converting to tapering doses of Dexamethasone.	

Other modes of treatment that can be considered,

	I. **IV Tocilizumab*** ○ Dose: 8mg/kg single dose (max: 800 mg/dose) II. **Convalescent Plasma*** **Consult infectious diseases physician before using these drugs.* **C) Thrombo-embolism treatment** Refer to section *Prophylaxis therapy against VTE.* Check medication list for possible drug-drug interactions[2]
5	Refer to Annex 29: Intensive Care Preparedness and Management Guidelines.

3.1 Prophylaxis therapy against Venous Thromboembolism (VTE)

All patients in **Category 4 and Category 5** should receive standard prophylactic anticoagulation with Low-molecular-weight heparin (LMWH) in the absence of any contraindications (active bleeding or platelet count less than 25,000). In renal impairment, dosage adjustment may be needed.

For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices)

Table 3: Prophylaxis Dose of Anticoagulants

	CrCl >30ml/min	**CrCl <30ml/min**
Standard Risk Patient*	**LMWH Enoxaparin 0.5mg/kg daily**	SC UFH 5000u bd to tds
High Risk Patient **Eg ICU patients**	**LMWH Enoxaparin 0.5mg/kg bd**	No clear data on dose and choice but UFH is preferred or reduced dose of enoxaparin 20 mg daily or 40 mg EOD

* Higher doses to be considered in patients more than 100kg

** Creatinine clearance > 30ml/min – higher doses of LMWH may be needed if patient is more than 100kg

3.2 Deep Vein Thrombosis (DVT):

If possible, obtain a Venous Doppler study to evaluate asymmetric limb pain or oedema.

If DVT is present, start full dose anticoagulation (LMWH preferred).

If unable to perform ultrasound and clinical suspicion for DVT is high, full dose anticoagulation (unless contraindicated) is recommended.

3.3 Pulmonary Embolism (PE)

Consider Pulmonary Embolism and treat with full dose of anticoagulation in patients with:

Marked increase/rising D dimer
AND
a. Acute worsening of hypoxeamia, blood pressure, tachycardia with imaging findings NOT consistent with worsening COVID-19 pneumonia
OR
b. Evidence of acute, otherwise unexplained right heart strain, or intra-cardiac thrombus
OR
c. Clotting of vascular devices (eg venous, arterial and dialysis catheters/ tubing)

If unable to perform CT Pulmonary Angiography (CTPA), Ultrasound or Echocardiogram and clinical suspicion for PE remains high, full dose anticoagulation (unless contraindicated) is recommended.

Table 4: Clinical Monitoring in COVID-19

Clinical Stage		Clinical monitoring	Laboratory and Radiological Monitoring
1.	**Asymptomatic**	Vitals signs monitoring Twice a day Doctors review bd	FBC, RP, LFT, RBS (or capillary blood sugar) at baseline Repeat bloods as indicated CXR
2.	**Symptomatic without pneumonia**	Vitals signs monitoring 8-12hrly Doctors review bd	FBC, RP, LFT, CRP/LDH, RBS (or capillary blood sugar) at baseline Repeat FBC, CRP/LDH if patient has any warning signs Rest, repeat as indicated CXR Repeat CXR if patient develops warning signs Baseline ECG for those with risk factors, repeat as necessary

3.	**Pneumonia not requiring oxygen**	Monitoring as per category 2, however, in the presence of Risk Factors vital signs monitoring 6-8hrly If further clinical deterioration, increase frequency of monitoring Doctors review TDS	FBC, RP, LFT, CRP/LDH, RBS (or capillary blood sugar) at baseline If any warning signs – repeat daily (FBC, CRP/LDH) Rest, repeat as indicated Baseline ECG for those with risk factors. Repeat as necessary CXR Repeat CXR if patient develops warning signs
4.	**Pneumonia requiring oxygen**	Refer ICU Vitals signs monitoring 4hrly Doctors to review 4-6 hrly	FBC, RP, LFT, CRP/LDH, RBS (or capillary blood sugar) at baseline Daily FBC, RP, CRP/LDH As indicated – LFT, Ferritin Procalcitonin*, D dimer CXR at first presentation Repeat CXR if further deterioration Baseline ECG. Repeat as necessary **Procalcitonin can be raised in both bacterial infection and CRS*
5.	**Critically ill patient**	*As per local standardized ICU monitoring protocol*	

B. Clinical Management of Confirmed COVID-19 Case in Paediatrics

1. Introduction

Coronavirus infection by this novel virus of SARS-CoV-2 was first reported among adults and children in late December 2019 in Wuhan, China. Multiple large epidemiological studies from China, Europe and United States, show the disease is predominantly mild, self-limiting clinical disease in children unlike adult counterpart

The clinical staging from stage 1-2 are of mild disease, whereas starting from stage 3, there is already organ involvement with lung being the major organ implicated starting with pneumonia (Refer table 1).

Table 1: Clinical staging of Syndrome associated with COVID-19

Clinical stage			
1	Mild Disease	Asymptomatic	• Only RT-PCR test positive
2		Symptomatic, No pneumonia	• Upper respiratory tract (URT) symptoms (e.g., pharyngeal congestion, sore throat, cough or fever) for a period less than 7 days.
3	Moderate disease	Symptomatic, pneumonia	• URT symptoms with others like vomiting, diarrhea, abdominal pain, myalgia, loss of smell/taste. • Signs of increase work of breathing and increase respiratory rate, but no hypoxemia (i.e. NO oxygen requirement)
4	Severe disease	Symptomatic, Pneumonia, requiring supplemental oxygen **OR** New requirement of	• Tachypnoea* with hypoxemia (SpO2<94% on room air) • CNS effect: Lethargy, decreased level of consciousness, seizure • GI effects: Dehydration,

		supplemental oxygen or increase requirement from baseline without need for non-invasive or invasive ventilation).	difficulty feeding, raised liver enzymes • Myocardial effect: Raised Creatinine Kinase, Troponin
5	Critical Illness	Critically Ill with multiorgan involvement OR New or increased need for non-invasive or invasive ventilation, sepsis, multi-organ failure or rapidly worsening clinical disease.	Rapid disease progression with: • Respiratory failure requiring mechanical ventilation (acute respiratory distress syndrome (ARDS), • Persistent hypoxemia • Septic shock • Organ failure requiring invasive monitoring and mechanical ventilation (myocardial injury/heart failure; liver injury/ coagulation dysfunction; kidney injury)

*Tachypnoea is defined as:
RR≥ 60 for infants < 2 months
RR≥ 50 for infants 2-11 months
RR≥ 40 for children ≥ 1 year of age

2. Laboratory Investigation

The majority of children are asymptomatic (stage 1) or mildly symptomatic (stage 2) disease. Exclude alternative diagnosis with relevant blood test; no additional blood test is required beyond those.

For children with pneumonia without the need of oxygen supplementation (stage 3); routine bloods of FBC, RP can be taken as of usual practice with tests to exclude alternate diagnosis. Need to use clinical judgments when radiological tests are ordered.

For confirmation of COVID-19 infection, the standard is respiratory samples of nasopharynx (NP) or oro-pharynx (yield better for NP) or best, combined naso-

oropharynx for RT-PCR. If the child is intubated, the preferred sample is of lower respiratory tract (LRT) e.g. tracheal aspirate.

If the children are presenting or deteriorating with severe features consistent with ARDS or shock (critical); samples of respiratory and blood should be taken for other virology testing or common bacterial infections of childhood (just like pre COVID era, if not taken yet) and markers to suggest disease progression.

Monitor for cytokine release syndrome (CRS) by looking for drop in blood pressure (hypotension), worsening hypoxemia and biomarkers. Warning signs reported in adults are persistent or recurrence of fever, dropping absolute lymphocyte count (ALC) and increasing CRP and tachycardia.

Table 2: Laboratory test for children with stage 4 and 5 (Severe and Critical illness)

DIAGNOSTIC TESTS	
Hematology/ Biochemistry	• FBC, Renal profile, LFT with AST/ALT, LDH, Ferritin, *CRP • Coagulation profile (including D-dimer) when indicated • Troponin (if myocardial injury)
Virology panel of respiratory samples (LRT is preferred)	• SARI panel (21 pathogens are currently detected including Influenza, Mycoplasma, AdenoV and Enterovirus
Microbiology	• Blood Culture & Sensitivity • Urine Culture & Sensitivity • CSF Culture & Sensitivity (when indicated) • HIV test (if considering Lopinavir/Ritonavir)
Radiology	• Chest X-ray (or Ultrasound of Thorax) • Echocardiogram (heart involvement/ KD)
Others	• In young children (<2 years); consider T&B cell (lymphocyte subset) to exclude immunodeficiency • Rectal swab for enterovirus • HSV 1/2 • CSF for meningitis-encephalitis panel

Note:

- For children with high risk of disease progression: need to obtain baseline FBC, CRP, D-dimer, ferritin, lactate dehydrogenase (LDH) and monitor them (2-3 times per week) if there is concern for worsening disease.
- For stage 4 and above: need also baseline LFT/AST/ALT with RP and monitoring them 2-3 per week if there is concern for worsening disease
- Certain diagnostic tests are decided on case by case basis and shall be performed when indicated.

3. Treatment

There is no evidence of any specific, established therapy being effective at treating children with COVID-19 at the present time. The clinical presentation of COVID-19 in children overlaps with other common childhood illness and there is no specific clinical, radiological, or laboratory criteria that are specific enough to incriminate COVID-19 alone. Large epidemiological studies confirm that this infection typically runs as mild course in children hence supportive care alone is suggested for all cases including severe or critical (stage 4 and 5). Most children with COVID-19 improve with supportive care, even those with severe disease.

3.1 General Care for Child with COVID-19

a. Antipyretic
   - Fever can be reduced with use of acetaminophen (paracetamol) 15mg/kg/dose 6hrly or as needed (maximum dose of 75mg/kg/day or 4g/day) orally
   - Need to adjust when there is raised liver enzymes
b. Oxygen supplementation
   - Use low flow nasal cannula (LFNC) oxygen
   - If children are still hypoxic despite LFNC, high flow nasal cannula (HFNC) can be used, limit it preferably in negative pressure isolation room (since use of HFNC is considered aerosol generating procedure (AGP)
   - Routine blood gases are not needed. This can be done if despite HFNC, children appear to require further respiratory support. Capillary blood gas may be used to look at pH and pCO2.
c. Nasogastric feeding or intravenous hydration started when child is unable to tolerate oral feeds.
d. Avoid aggressive fluid management which can impair alveolar oxygen exchange.
e. Avoid use of nebulization. When B2 agonist is needed, deliver through spacer by using metered-dose inhaler (MDI).

f. In critical (stage 5) cases, additional pressure and ventilatory support may be required including intubation.
g. Intubation should be performed by the most experienced provider with appropriate Personal Protective Equipment in place. (Refer Guidelines COVID-19 Management in Malaysia Annex 8**:** The Infection Prevention and Control

3.2 Use of Antibiotics

Antibiotics are not recommended to treat cases of COVID-19 unless there is suspicion of bacterial co-infections. Early studies from China found the rate of secondary bacterial infections to be low. When there is evidence of secondary bacterial infections, appropriate antibiotics should be administered pre-emptively, without waiting for confirmatory results/tests.

a. For pneumonia:
   Mild cases : Oral Amoxycillin 80-90mg/kg/day in 2 divided doses for 5-7 days

   Moderate cases : Cefuroxime 100-150mg/kg/day IV in 3 divided doses (max. 6gm/day)
   OR
   Amoxicillin/clavulanate 30mg/kg/dose IV q8h (max.1.2gm/dose)

   For atypical pneumonia:
   Azithromycin 10mg/kg/dose (max.500mg) PO q24h on Day1; then 5mg/kg/day (max. 250mg) on Day 2-5.

b. For Sepsis, treat with an IV third-generation Cephalosporin
   Cefotaxime 50mg/kg/dose IV q6h (max. 2g/dose or 8gm/day)
   OR
   Ceftriaxone 50mg/kg/dose q12-24h

   ADD Clindamycin 20-40mg/kg/day IV in 3-4 divided doses (max.2.7gm/day) WHEN Streptococcal/Staphylococcal TOXIC SHOCK SYNDROME is suspected. **(Adjust antibiotics when culture and sensitivity are known)**

c. Consider antibiotics
   If a child is unusually sick on admission/Day 1(particularly fever and /or still on oxygen) or if there is a clinical deterioration or if they are from high risk groups.

Children with COVID-19 have fever that generally subside within 3 days.
Given the relatively mild disease associated with this virus, it is important to consider alternative diagnoses in children presenting as unwell following the same management practices in place prior to pandemic.

3.3 Use of Steroids

The use of steroids is not routinely recommended unless for other established indication e.g. acute exacerbation of asthma. The RECOVERY trial in COVID-19 in adults revealed a reduction in 28-day mortality in those receiving invasive ventilation or oxygen in combination with dexamethasone. This benefit was not seen in patients receiving dexamethasone that did not require oxygen support. This trial, however did not include significant number of children hence caution is needed to extrapolate the results to children infected with this virus.

Situations where steroids can be considered are:

a. Underlying medical conditions where steroid is needed (e.g., exacerbation of bronchial asthma, relapse nephrotic syndrome or on maintenance therapy for specific disease, {continue as per usual practice})
b. Stage 5
c. Stage 4: children who require increasing supplementary oxygen support or have risk factors for disease progression (refer to this special group*)
d. Worsening lung function at least 7 days from beginning of symptoms in association with marked alteration or increasing levels of inflammatory markers

Use low dose glucocorticoids at shorter duration to prevent secondary complication especially bacterial superinfection. Should not use steroid on children who do not require oxygen or only low levels of oxygen (e.g. nasal canula)

Steroid	**Dose**
Dexamethasone (IV or oral)	0.15mg/kg/dose once daily (max:6mg)
Methylprednisolone (IV)	0.8/kg once daily (max:32mg)
Prednisolone (orally/ nasogastric tube)	1mg/kg once daily (max :40mg)
Hydrocortisone	1.3mg/kg IV every 8hours (max:50mg; max. total daily dose 150mg)
Duration: 5 days	

3.4 Use of Intravenous Immunoglobulin (IVIG)

Routine use of IVIG has not been shown to be of any benefit to individual with COVID-19. The only other situation where it can be considered is in Kawasaki-like (KD) syndrome, toxic shock syndromes or moderate to severe MIS-C.

IVIG	**Dose**	
KD -like features	2gm/kg given over 8-12 hours (single infusion)	
Patients with significant LV dysfunction	1gm/kg over 8-12 hours Day 1; 0.5mg/kg over 8-12 hours Day 2-3	Caution for fluid overload hence divided doses over 3 days.

3.5 Use of Specific Anti-Viral and Immunomodulators against COVID-19

Supportive care alone is appropriate in majority of children with severe form of COVID-19. There are currently no Food and Drug Administration (FDA) approved drugs for the treatment of COVID 19. Use of anti-viral should be considered on a case by case basis (specific group or overall risk of progression to more severe form) in:[6]

a. **Stage 4** where the child exhibits new requirement for supplemental O2 or increase from baseline without new or increased need for ventilatory support (invasive or non-invasive)
b. **Stage 5** (critical stage) where there is new or increased need for non-invasive/invasive ventilatory support, sepsis, multiorgan failure, or rapidly worsening clinical status.

Most experts suggest use of potentially active anti-viral drugs as part of clinical trials. Pediatrician should always be guided by principle of do no harm when considering anti-viral therapy reserving them only for those children in whom benefit outweighs the risk of toxicity.

The preferred anti-viral agent is:

a. Remdesivir (not available yet)
b. The use of Lopinavir/Ritonavir can be considered when Remdesivir not available[14]
   Randomized controlled trial (RCT) in adult demonstrated no difference in time to clinical improvement or virologic outcome by use of this protease inhibitor. Multicenter panel from Paediatric Infectious Disease are divided in use of this HIV drug BUT united against the use of combination of Lopinavir/Ritonavir with Ribavirin.[6]

Table 3: Treatment Regime of Anti-viral agents for Paediatric COVID-19 cases (listed not on any particular order)

<table>
<tr><th>Agent</th><th>Paediatric Dose/Duration</th><th>Comment</th></tr>
<tr><td>Remdesivir</td><td>Body weight <3.5kg to <40kg:
5mg/kg IV loading dose (30-120 minutes); followed by 2.5mg/kg/dose IV (30-120 minutes) q24h

Body weight >40kg:
200mg IV loading dose(30-120minutes) on D1; followed by 100mg IV (30-120minutes) q24hr</td><td>• Duration:5-10 days (shorter i.e. 5 days for fast responders)
• Monitor liver functions
• Need adjustment in renal impairment

Need written consent.</td></tr>
<tr><td>Lopinavir-Ritonavir

Syrup formulation need to be kept in fridge. it has 42% ethanol and propylene glycol.

Tablet:
200mg/50 mg readily available as hiv treatment drugs.
(100mg/25mg-paediatric tablet- kpk item)</td><td>Neonates above 14 days ≥ 42 weeks and children:

Lopinavir 300mg/m^2 /dose (max 400mg) PO twice a day

a. Syrup formulation:
<table>
<tr><th>Body weight</th><th>Dose</th></tr>
<tr><td>3 – 5kg</td><td>1ml 12hrly</td></tr>
<tr><td>6 – 9kg</td><td>1.5ml 12hrly</td></tr>
<tr><td>10 – 13kg</td><td>2.0ml 12hrly</td></tr>
<tr><td>14 – 19kg</td><td>2.5ml 12hrly</td></tr>
<tr><td>20 – 24kg</td><td>3.0ml 12hrly</td></tr>
</table>
b. Tablet (200mg/50mg)
>35kg: 400mg/100mg12hrly</td><td>• Duration:7-14 days
• Not recommended with ribavirin
• Side effects: Hepatotoxicity, pancreatitis, glucose intolerance, QT prolongation, lipid elevation and fat redistribution
• Check HIV status prior to commencement.
• Drug-drug interaction via cytochrome P450

Need written consent.</td></tr>
</table>

3.6 Immunomodulatory

Pathogenesis of this virus is not only through direct invasion via ACE2 receptors. This is expressed in various organ including lung. It is also immune mediated; proposed mechanism in severe cases is “cytokine storm “where various cytokines are released including IL-6. Hence the use of immune modulators as

adjunct therapy in certain circumstances where this phenomenon is suspected. Just like use of anti-viral, the risk against benefit need to be considered before starting this treatment. Decision made on case-by-case basis according to disease severity after discussion with paediatric infectious diseases specialists.

Use is considered only after end of initial phase of high viral load of COVID-19 (afebrile >72hours and /or at least 7 days after the onset of symptoms)

Agent	Formulation	Dose	Duration	Comment
TOCILIZUMAB	Body weight <30kg: 20mg/ml single dose vials. Dilute to 50ml with 0.9% Sodium Chloride	12mg/kg	If no improvement at 12 hours, repeat with same dose	• Need to discuss with Paediatric Infectious Disease Consultant
	Body weight >30kg: 20mg/ml single dose vials. Dilute to 100ml with 0.9% Sodium Chloride	8mg/kg (max 800mg)	If no improvement at 12 hours, repeat with same dose	• Need to discuss with paediatric infectious disease consultant • Side effects: GI perforation, Anemia, Hepatitis, Infusion related risk, risk of secondary infection.

3.7 Venous thromboembolism (VTE) prophylaxis

A diagnosis of COVID-19 among children should not influence the decision to start VTE prophylaxis. Anticoagulant or anti-platelet should not be used to prevent arterial thrombosis outside of the usual standard care for patients without COVID-19. Preventive therapy can be considered in children with:[14]

a. MIS-C
b. Children with KD like features or significant LV dysfunction

Agent	Dose
SC enoxaparin	100-200 U/kg day

3.8 Convalescent plasma

The safety and effectiveness of COVID-19 convalescent plasma have not been evaluated in children. Clinical trials are ongoing.[13]

4. Special Considerations for COVID-19 Infection and Treatment Including New Clinical Syndromes

Some paediatric populations should be considered at higher risk for severe COVID-19 related disease even though there is no clear evidence to confirm this. Report from multicenter panel from Pediatric Infectious Diseases Society of North America, suggest that certain group of children might have higher risk of mortality or morbidity when they contract this viral illness.[6] Most of the evidence is insufficient and extrapolation from adult data are used to say which group of children might be more likely to experience severe illness. Recently a multicenter trial among children and adolescent have added more information.[12] Any child with medical illness are at risk by looking at experience with other respiratory tract infections. **But specific group who might have risk of disease progression and need consideration for anti-viral as recommended by expert panel are**:*[6]

- Severely immunocompromised children (e.g. hematopoietic/solid organ transplant recipient, children receiving anti-cancer chemotherapy, Primary immunodeficiency, other immunosuppressive medications and conditions (e.g. high dose glucocorticoids use)
- Children with severe underlying cardio-vascular disease (including not limited to any cardiomyopathy, NYHA/Ross class ii-iv heart failure etc.)
- Children with severe underlying pulmonary disease (including not limited to severe persistent asthma, neuromuscular disease resulting in airway clearance/cough [e.g.SMA, Duchenne' or other muscular dystrophies], severe chronic respiratory disease [e.g. cystic fibrosis, bronchopulmonary dysplasia, interstitial lung disease etc.])

    - There is insufficient evidence to suggest that young age alone is a risk factor for severe COVID-19.
    - Children with risk factors recognized in adults, including obesity, diabetes, and hypertension, may also be at risk, although there are no published data supporting this association and insufficient data to guide therapy.

4.1 New Syndrome of COVID-19

Overall, several large epidemiological studies suggest COVID-19 is usually a mild disease in children, although there are reports of children with COVID-19 requiring intensive care unit (ICU)-level care. Recently, SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children [MIS-C]; also referred to as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 [PIMS-TS].Early report from United Kingdom document children presenting with incomplete Kawasaki disease (KD) or toxic shock syndrome.

Most PMIS-TS cases have occurred in older children and adolescents who were previously healthy. Black and Hispanic children appear to be disproportionally affected. By contrast, classic KD typically affects infants and young children and has a higher incidence in East Asia and in children of Asian descent.

The pathophysiology of MIS-C is not well understood. A postinfectious process is suggested, based on the timing of the rise of these cases relative to the peak of COVID-19 cases in the communities where it was reported. Many affected children have negative polymerase chain reaction (PCR) testing for SARS-CoV-2 but have positive serology, a finding that further supports the hypothesis that MIS-C is related to immune dysregulation occurring after acute infection has passed.

Royal College of Paediatrics and Child Health published a guidance document on the clinical management of children presenting with PIMS-TS on 1st May 2020 and proposed the following case definition.

Case definition of Paediatric Multisystem Inflammatory Syndrome (PMIS-TS)

a. A child presenting with persistent fever, inflammation (Neutrophilia, elevated CRP, and Lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features.[7]This may include children fulfilling full or partial criteria for Kawasaki disease (refer Table 4 and 5)
b. Exclusion of other microbial cause including bacterial sepsis, Staphylococcal or Streptococcal shock syndromes, and infections associated with myocarditis such as enterovirus.
c. SARS-CoV-2 PCR testing may be positive or negative.

These children need to be managed in intensive care unit and peadiatric infectious diseases specialist/cardiologist/ rheumatologist involvement sought early in course of disease. Further details can be found at

https://picsociety.uk/news/pics-statement-regarding-novel-presentation-of-multi-system-inflammatory-disease/

4.2 Management of Paediatric Multisystem Inflammatory Syndrome

All children should be treated as suspected COVID-19. Epidemiological links need to be looked for whenever possible. Appropriate swabs of respiratory tract (lower respiratory tract preferable once intubated) for SARS-CoV-2 need to be sent as soon as possible to virology lab.

Blood culture should be sent prior to starting antibiotics for toxic and/ shock syndromes. For myocarditis, other than sending cardiac biomarkers of Troponin, Creatinine kinase and CK-MB, need also viral studies for e.g. Enterovirus 71, Coxsackie virus, Adenovirus and others like mycoplasma serology.

This is ONE condition where IVIG use should be considered.

a. For Kawasaki disease: Use IVIG and anti-platelet therapy of aspirin
b. For Toxic shock syndrome: IVIG as an adjunct; 1g/kg on D1, followed by 0.5mg/kg on 1-2 subsequent days.
c. For IVIG refractory condition: Methylprednisolone 2mg/kg/day in 2 divided doses; followed by oral equivalent dose of prednisolone and taper down slowly over few weeks.
d. For life threatening circumstances higher doses of Methylprednisolone is required.

Need to discuss with paediatric ID specialist/cardiologist/rheumatologist.

Table 4: Diagnostic criteria for Kawasaki disease (KD) °

Fever lasting at least 5 days
At least 4 out of the 5 of the following: • Bilateral non-purulent conjunctivitis • Mucosal changes of the oropharynx (injected pharyx, red lips, dry fissured lips, strawberry tongue) • Changes in extremities (oedema and or erythema of the hands or feet, desquamation, beginning periungally) • Rash (usually truncal), polymorphous but non vesicular • Cervical lymphadenopathy
Illness not explained by other disease process *Adapted from Paediatric protocols for Malaysian Hospital, 4th edition*.

Table 5: Clinical and laboratory features of PMID-KS

Clinical
All: • Persistent fever with temperature >38.5°C **Most:** • Oxygen requirement • Hypotension **Some:** • Abdominal pain • Confusion • Conjunctivitis • Cough • Diarrhoea • Headache • Lymphadenopathy • Mucus membrane changes • Neck swelling • Rash • Respiratory symptoms • Sore throat • Swollen hands and feet • Syncope • Vomiting

Laboratory
All: • Abnormal Fibrinogen • High CRP • High D-Dimers • High ferritin • Hypalbuminaemia • Lymphopenia • Neutrophilia in most – normal neutrophils in some • Absence of potential causative organisms (other than SARS-CoV-2 **Some:** • Acute kidney injury • Anaemia • Coagulopathy • High IL-10 & 6 (if available) * • Neutrophilia • Proteinuria • Raised CK • Raised LDH • Raised triglycerides • Raised troponin • Thrombocytopenia • Transaminitis

Imaging and ECG
• Echo and ECG: myocarditis, valvulitis, pericardial effusion, coronary artery dilatation • CXR – patchy symmetrical infiltrates, pleural effusion • Abdominal U/S – colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly • CT thorax – may demonstrate coronary artery abnormalities if done with contrast

Adapted from RCPCH Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19

5. Criteria for discharge from infectious diseases ward/isolation facilities.

A child admitted for COVID-19 can be discharged when:

a. For **symptomatic patients,** at least 10 days have passed since symptom onset **AND** at least 24 hours have passed since resolution of fever without the use of fever-reducing medications **AND** other symptoms such as dyspnoea, cough have improved.
b. For **asymptomatic patients**, maybe discharged 10 days after the date of their first positive RT-PCR test for SARS-CoV-2.
c. For immunocompromised hosts, decision to release them from COVID-19 pathway should be taken on case to case basis.

Evidence of viral clearance from upper respiratory tracts is not needed anymore. Test to document clearance of virus might be done on case-to-case basis taking into consideration risk versus benefit of doing such test in young children.

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