Interim Recommendation on Clinical Management of Paediatric Patients of Coronavirus Disease 2019 (COVID-19) Infection

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Author	HA Task Force on Clinical Management on Infection (TFCM)
Custodian	Central Committee on Infectious Diseases and Emergency Response (CCIDER)
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Table of Contents

1. Background

1.1 For paediatric patients infected with COVID-19, cases reported in the current literature are mild in clinical severity, and there is no evidence-based treatment regimen. The present treatment recommendations take reference from the adult interim management guideline and the WHO interim guideline. Specifically, the Hong Kong adult interim management guideline from Ad hoc Task Force on Clinical Management (TFCM) on Infection recommend consideration for specific anti-novel coronavirus treatment while WHO only recommended supportive treatment. Both TFCM on Infection and our group recognized that the proposed regimens are based on evidence extrapolated from research on other coronaviruses, expert opinion, as well as the availability of therapeutics in Hong Kong.

2. Infection of COVID-19 in paediatrics

2.1 Infection with SARS-CoV was much milder in paediatrics when compared to adults, and from limited information to date appears to be the similar with COVID-19.

3. Anti-viral treatment

3.1 Taking reference that paediatric infection with SARS-CoV was associated with more severe disease (although no mortality) in children ≥12 years of age, an age-stratified approach for specific anti-viral treatment may be considered.

3.2 Age <12 years old and stable clinical condition:

3.2.1 Investigation after admission

(i) CBP D/C, ESR, CRP, LRFT, LDH, ABG (if indicated);

(ii) Chest X-ray (CXR) +/- High Resolution Computed Tomography (HRCT) of thorax (if indicated);

(iii) Prescription of empirical antibiotics treatment will be at the discretion of in charge paediatrician;

3.2.2 Close monitor vital signs and organ functions and recognize signs for clinical deterioration

(i) If clinically stable, continue monitoring as in 4.

(ii) If clinically deteriorated e.g. increase oxygen requirement,

progressive CXR infiltrates, extensive pulmonary involvement in HRCT thorax. Consider anti-viral treatment. Proceed to 3.3.

3.3 Age ≥ 12 years old, Age < 12 year old with unstable clinical condition or severe pneumonia on admission; clinical deterioration during hospitalization. Anti-viral treatment may be considered.

3.3.1 Pre-treatment laboratory tests: Blood for: CBC D/C, ESR, CRP, LRFT, random glucose, clotting profile, LDH, HBsAg, Anti-HCV, Anti-HIV, (+/- arterial blood gas if indicated);

3.3.2 Chest X-ray +/- High Resolution Computed Tomography of thorax (if indicated);

3.3.3 Baseline Electrocardiogram (if pre-existing cardiac abnormalities or disease). For patients with underlying pre-existing cardiac disorders, follow-up monitoring of the cardiac condition is recommended;

3.3.4 Consider specific treatment when the diagnosis of COVID-19 is made:

(i) Kaletra (Lopinavir / Ritonavir) BD for 14 days

Plus or minus

(ii) Interferon beta-1b* (Betaferon) 8 million IU (equivalent to 250micrograms) subcutaneous (SC) every alternate day for 3 doses {i.e. on D 1-2, D2-3 & D5-6}

- *Interferon beta-1b not licensed for <12 year old
- To achieve adequate efficacy, no dose titration is recommended in treatment of COVID-19 infection. However patient should be closely monitored for severe side effects.

3.3.5 Dosage of Kaletra (Lopinavir/Ritonavir, LPV/r):

(i) **<u>Do not administer</u>** Kaletra to neonates before postmenstrual age of 42 weeks and a postnatal age of at least 14 days

(ii) Three preparations available in HA:

- Oral solution: [Kaletra] Lopinavir 80 mg/ml and ritonavir 20 mg/ml
  - ➢ Reserve syrup formulation of Kaletra for patients in PICU or patients with swallowing difficulty.
- Tablets: (LPV/r tablets must be swallowed whole. Do not crush or split tablets)
  - ➢ [Kaletra] Lopinavir 200 mg/ritonavir 50 mg
  - ➢ [Kaletra] Lopinavir 100 mg/ritonavir 25 mg

(iii) Dosage:

- Infant (Aged 14 Days–12 Months) Dose:
  - LPV/r 300 mg/75 mg per m^2 BD. This approximates LPV/r 16 mg/4 mg (both per kg) BD.
- Child and Adolescent Dose (Aged >12 Months to 18 Years):
  - LPV/r 300 mg/75 mg per m^2 BD (maximum dose LPV/r 400 mg/100 mg BD).
  - For patients weighing <15 kg, this approximates LPV/r 13 mg/3.25 mg (both per kg) BD.
  - For patients weighing ≥15 kg to 45 kg, this dose approximates LPV/r 11 mg/2.75 mg (both per kg) BD.

3.3.6 Omission of Interferon beta-1b:

(i) To omit the remaining dose of Interferon beta-1b when the symptom onset is approaching 7 days, e.g. if the patient presents on day 6 of symptoms onset, only one dose of interferon should be given;

(ii) If the patient presents with symptoms more than 7 days, only Kaletra should be given.

3.3.7 Pre-treatment check-list:

(i) Check presence of any drug interaction with concomitant medications (especially with ritonavir);

(ii) Pregnancy test for adolescent girls before initiating interferon (contraindication);

(iii) Obtain consent for treatment:

- Unlicensed indication and the treatment is experimental, treatment may improve or worsen infection,
- The patient and/or parents should be explained on the side effects of treatments,
- Contraindications:
  - Interferon beta-1b: history of hypersensitivity to interferon beta, albumin; pregnancy, decompensated liver disease, current severe depression and/or suicidal ideation
  - Kaletra: history of hypersensitivity to Lopinavir, Ritonavir. Avoid in patients with congenital long QT syndrome and cautious use in patients using other drugs that prolong QT interval.

4. Monitoring during treatment

4.1 Blood for CBP D/C, LRFT, LDH, CRP

4.2 Stool for RT-PCR nCoV-2019 if having GI symptoms

4.3 Repeat NPS + Throat swab (pooled specimens) OR NPA for RT-PCR COVID-19 (release of isolation order requires 2 negative specimens taken 24 hours apart).

4.4 2 negative stool specimens for RT-PCR COVID-19 are required for release of isolation order if the initial specimen(s) on admission tested positive.

4.5 Side effects from treatment.

4.5.1 Interferon beta-1b:

Most frequently observed side effects are a flu-like symptom complex e.g. fever, chills, arthralgia, malaise, sweating, headache, or myalgia; which is mainly due to the pharmacological effects of the medicinal product, and injection site reactions. Other side effects include neutropenia, thrombocytopenia, hepatotoxicity, thyroid dysfunction and drug-induced lupus. Severe adverse reactions manifested as acute anaphylaxis and psychiatric disorders were also reported.

4.5.2 Kaletra:

(i) Most common side effects include gastrointestinal upset (diarrhea, nausea and vomiting), liver function derangement, hypertriglyceridemia and hypercholesterolemia. Serious adverse reaction including prolonged QT interval, torsade de pointes and anaphylaxis reaction.

(ii) KALETRA oral solution contains approximately 42% (v/v) ethanol and approximately 15% (w/v) propylene glycol. Ethanol competitively inhibits propylene glycol metabolism, which may lead to propylene glycol toxicity due to impaired elimination in neonates. In neonates and infants 14 days to 6 months of age, especially for those with renal impairment, the total amounts of ethanol and propylene glycol delivered from all medications should be considered to avoid toxicity. They should be monitored for signs and symptoms of propylene glycol toxicity (e.g., increase in serum creatinine, seizures, cardiac arrhythmias, lactic acidosis, hyperosmolarity, stupor, and hemolysis).

5. Use of Corticosteroids

5.1 Routine use of corticosteroid is not recommended;

5.2 Stress dose steroids for refractory septic shock may be used for short period or other indications at the discretion of the in-charge paediatrician.

6. Use of adjunct treatment

6.1 There is **no** adjunct treatment recommended at this moment.

7. Psychological support

7.1 The patients are more prone to have symptoms of anxiety and/or depression, proactive psychological counselling and early intervention are needed.

8. Release of isolation order

8.1 To liaise with Medical Control Officer (MCO) of Centre for Health Protection (CHP) for release of isolation order when the patient is clinically ready for discharge and result of specimens on 4.3 & 4.4 tested negative

9. References

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