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

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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.

2. Taking reference that paediatric infection with SARS-CoV was associated with milder disease compared with adult counterparts, a conservative management approach will be adopted. Please consult PID specialist for specific anti-viral and immunomodulator treatment if considered necessary.

3. **Reporting**: Please report suspected cases fulfilling the reporting criteria of Coronavirus Disease 2019 (COVID-19) to the Central Notification Office (CENO) of CHP via NDORS. The case definition is available on the above website of CENO On-line (https://cdis.chp.gov.hk/CDIS_CENO_ONLINE/ceno.html). Both reporting criteria and case definition are subject to change upon availability of further epidemiological, clinical and virological data.

4. **Diagnosis:** Diagnosis can be established by either Rapid Antigen Test (RAT) or RT-PCR of SARS-CoV2.

5. **Investigation after admission** (if clinically indicated):
   (i) CBP D/C, ESR, CRP, L/RFT, LDH, CK, D-dimer, ABG;
   (ii) Chest X-ray (CXR)
   (iii) High Resolution Computed Tomography (HRCT) of thorax.
   (iv) Prescription of empirical antibiotics will be at the discretion of in charge paediatricians.

6. **Closely monitor** vital signs and organ functions e.g. anosmia, ageusia, etc.; and recognize signs for clinical deterioration including signs for clinical deterioration including croup, pneumonia, pulmonary embolism, central nervous system involvement, etc.
   (i) If clinically stable, continue monitoring.
   (ii) If clinically deteriorated e.g. increase oxygen requirement, progressive CXR infiltrates, extensive pulmonary involvement in HRCT thorax, change in mental status, repeated and / or prolonged seizure, etc discuss with PID

specialists for anti-viral and / or immunomodulation treatment.

7. **Antiviral treatment:** Unlicensed treatment should be given under ethically-approved clinical trial as far as possible. In the absence of appropriate clinical trials, the following treatment may be considered in patients having the following conditions with increased risk of severe disease.
   - Diabetes mellitus
   - Immunocompromised condition (congenital or acquired)
   - Underlying chronic illnesses
   - Autoimmune, autoinflammatory and immunodysregulatory conditions
   - Incomplete COVID-19 vaccination status
   - Obesity (body mass index of 30kg/m2 or higher)

8. **Antiviral treatment available in paediatric patients:**

   (i) <u>Paxlovid</u>
   - Paxlovid is a combination of nirmatrelvir, a SARS-CoV-2 main protease inhibitor that prevents viral replication, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor that is not active against SARS-CoV-2 but inhibits the metabolism of nirmatrelvir resulting in increased plasma concentration of nirmatrelvir.
   - Paxlovid may be used in paediatric patients (12 years of age and older weighing at least 40 kg).
   - Dosage and administration: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days.
   - Criteria for use
     - Incomplete COVID-19 vaccination, AND
     - Individuals with high risk factors (e.g. diabetes OR immunocompromised status etc. Please refer to Annex B)
   - Clinical consideration
     - Within 5 days of symptom onset, AND
     - Test positive (RAT/PCR), AND
     - SpO2 > 94% (room air), AND
     - With or without early pneumonic changes

- Exclusion criteria
  - Patients less than 12 years of age or weighing below 40kg
- Warnings and precautions:
  - The concomitant use of Paxlovid and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (Annex A)
  - Allergic Reactions/Hypersensitivity: Hypersensitivity reactions have been reported with Paxlovid. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxlovid and initiate appropriate medications and/or supportive care.
  - Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir.
  - HIV-1 Drug Resistance: Paxlovid use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.
- Adverse reactions
  - Dysgeusia, diarrhea, hypertension, and myalgia.
- Renal impairment: dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min): 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days. Paxlovid is not recommended in patients with severe renal impairment (eGFR <30 mL/min).
  - From operational perspectives, the most recent eGFR result within 1 year can be used for reference. For patients without recent eGFR result available, it is reasonable to choose full dose for healthy paediatric patients without known renal impairment.
- Hepatic impairment: Paxlovid is not recommend in patients with severe hepatic impairment (Child-Pugh Class C).
- Pregnancy consideration: There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have

not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug associated risk of miscarriage. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy. The use of nirmatrelvir and ritonavir should not be withheld from pregnant patients when the potential benefits outweigh the possible risks (NIH 2022).

- Breastfeeding consideration: Ritonavir is present in breast milk; excretion of nirmatrelvir is unknown. Lactation is not a contraindication for use (ACOG 2022; FDA 2021). According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother (FDA 2021).

(ii) <u>Remdesivir</u>

- Remdesivir is an antiviral and inhibits SARS-CoV-2 RNA polymerase which perturbs viral replication. Remdesivir is given intravenously, once daily after an initial loading dose.
- Remdesvir may be considered in severe paediatric Covid patients, with organ failure such as severe pneumonia (SaO2 < 94% on room air), encephalitis, myocarditis, etc. Because of the limited data, decision should be made case by case.
- Recommended dose for paediatric use of Redemsivir:
  - Paediatric patients weighing 3.5kg – 40kg:
    - IV: One dose of 5mg/kg on Day 1 followed by 2.5mg/kg on Day 2 and subsequent days.
  - Paediatric patients weighing >40kg, adult dose should be used:
    - IV: One dose 200 mg on day 1 followed by 100 mg for subsequent days.
  - (For patients who are not on ECMO or invasive mechanical ventilation, the duration of treatment is up to 5 days or until Day 10 if no symptomatic improvement is observed).
  - Remdesivir should be made up to the dilution volume with 0.9% saline and infused intravenously over 30 to 120 minutes.
- Significant adverse reactions that might be consider include:

- Cardiac effects: Postmarketing reports of bradycardia, including severe bradycardia (some fatal) and sinus bradycardia, have been reported in patients receiving remdesivir
- Hepatic effects: Mild to moderate (grades 1 to 2), reversible transaminase elevations, including increased serum alanine aminotransferase and increased serum aspartate aminotransferase, have been observed in healthy volunteers and patients with SARS-CoV-2. It is unclear if these effects are drug-related or related to SARS-CoV-2.
- Hypersensitivity and infusion related reactions: Hypersensitivity reactions, including anaphylaxis and infusion related reactions, have been reported during and following remdesivir administration. Patients may experience angioedema, bradycardia, diaphoresis, dyspnea, fever, hypertension, hypotension, hypoxia, nausea, rash, shivering, tachycardia, and wheezing. Slower infusion rates (maximum infusion time of up to 120 minutes) may be considered in patients to potentially prevent hypersensitivity or infusion related reactions.

- Use in circumstances of hepatic and renal impairment:

  Hepatic Impairment:

  ALT>= 5 times upper limit, use is not recommended.

  ALT< 5 times upper limit, use if therapeutic benefits outweigh the risk.

  Renal impairment:

  eGFR >= 30ml/minute. No dosage adjustment recommended.

  eGFR <30ml/minute. No formal safety or pharmaceutical data are available for patients with kidney impairment or who are receiving renal replacement therapies. Use is not recommended by the manufacturer. However, significant toxicity with a short duration of therapy (e.g. 5 to 10 days) is unlikely; benefits may outweigh the risks in selected patients.

(iii) Information and consent form

- As there is no consensus on international recommendation of using specific antiviral agents of treatment of Covid, it is necessary to sign an information

and consent form for experimental treatment prior to use. A copy of the consent form dated 21 September 2021 was attached in the appendix section.

9. **Immunomodulation Therapy:** Please consult PID Specialists if this considered necessary.

10. **Use of adjunct treatment:** There is **no** adjunctive treatment recommended at this moment.

11. **Psychological support:** The patients are more prone to have symptoms of anxiety and/or depression, proactive psychological counselling and early intervention are needed.

12. **Release of isolation order:** Follow the update arrangement by the Centre for Health Protection.

13. **Out-patient Follow Up:** To consider follow up patients for: persistence of symptoms e.g. anosmia, ageusia, decrease in exercise tolerance; or occurrence of new symptoms.

14. **References:**

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4. Melissa Chima, et. al. COVID-19–Associated Pulmonary Embolism in Pediatric Patients. Hospital Pediatrics Volume 11, Issue 6, June 2021. DOI: https://doi.org/10.1542/hpeds.2021-005866
5. Interim Recommendation on Clinical Management of Adult Cases with

Coronavirus Disease 2019 (COVID 19), HA Central Committee on Infectious Diseases and Emergency Response (CCIDER). Effective since 11 March 2022.

6. J.H. Beigel, et. al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med 2020; 383: 1813-26. DOI: 10.1056/NEJMoa2007764.
7. NIH COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/
8. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. Available at: https://www.fda.gov/media/155050/download
9. Nirmatrelvir and ritonavir (United States and Canada: Authorized for use): Drug information. Uptodate (accessed 7 March 2022)

Acknowledgement: Mr. Burns Wong, Clinical Pharmacist, Princess Margaret Hospital

Annex A. Important Drug Interactions with Paxlovid*

Paxlovid is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions:

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

Paxlovid is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. Paxlovid cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (hypericum perforatum)

*Please refer to Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid (Table 1) for listing of clinically significant drug interactions (Available at: https://www.fda.gov/media/155050/download)

Annex B. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19

1. **Higher risk** for severe COVID-19 outcomes
   - Cancer
   - Cerebrovascular disease
   - Chronic kidney disease*
   - Chronic lung diseases limited to:
     - Interstitial lung disease
     - Pulmonary embolism
     - Pulmonary hypertension
     - Bronchiectasis
     - COPD (chronic obstructive pulmonary disease)
   - Chronic liver diseases limited to:
     - Cirrhosis
     - Non-alcoholic fatty liver disease
     - Alcoholic liver disease
     - Autoimmune hepatitis
   - Cystic fibrosis
   - Diabetes mellitus, type 1 and type 2*
   - Disabilities
     - Attention-Deficit/Hyperactivity Disorder (ADHD)
     - Cerebral Palsy
     - Congenital Malformations (Birth Defects)
     - Limitations with self-care or activities of daily living
     - Intellectual and Developmental Disabilities
     - Learning Disabilities
     - Spinal Cord Injuries
     - (For the list of all conditions that were part of the review, https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html#accordion-1-card-1)
   - Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)
   - HIV (human immunodeficiency virus)
   - Mental health disorders limited to:

  - Mood disorders, including depression
  - Schizophrenia spectrum disorders
- Neurologic conditions limited to dementia
- Obesity (BMI ≥30 kg/m2)*
- Primary Immunodeficiencies
- Pregnancy and recent pregnancy
- Physical inactivity
- Smoking, current and former
- Solid organ or hematopoietic cell transplantation
- Tuberculosis
- Use of corticosteroids or other immunosuppressive medications

2. **Suggestive higher risk for severe COVID-19 outcomes**
   - Children with certain underlying conditions
   - Overweight (BMI ≥25 kg/m2, but <30 kg/m2)
   - Sickle cell disease
   - Substance use disorders
   - Thalassemia

3. **Mixed evidence**
   - Alpha 1 antitrypsin deficiency
   - Asthma
   - Bronchopulmonary dysplasia
   - Hepatitis B
   - Hepatitis C
   - Hypertension*

Footnote: * indicates underlying conditions for which there is evidence for pregnant and non- pregnant people

(Source: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. US CDC. Updated Feb. 15, 2022. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html)