MINISTRY OF HEALTH
MALAYSIA

CLINICAL MANAGEMENT OF CORONAVIRUS DISEASE 2019 (COVID-19) IN PAEDIATRICS

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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 counterparts.
- However, the disease is still evolving and most of the paediatric literature is still in infancy at this point in time.

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 supplemental oxygen or increase requirement from baseline without need for non-invasive or invasive ventilation)	• Tachypnoea* with hypoxemia (SpO2<94% on room air) • CNS effect: Lethargy, decreased level of consciousness, seizure • GI effects: Dehydration, difficulty feeding, raised liver enzymes • Myocardial effect: Raised Creatinine Kinase, Troponin

Table 1: Clinical Staging of Syndrome Associated with COVID-19 (cont…)

CLINICAL STAGE			
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

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 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) 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 virology testing and markers to suggest disease progression (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

Note:

- For stage 4: Baseline tests of FBC, CRP, LFT/AST/ALT, RP and if progression of disease, other *inflammatory markers
- Certain diagnostic tests are decided on case by case basis and shall be performed when indicated.

Treatment

- There is no evidence of any specific, established therapy being effective at treating children with COVID-19 at the present time.
- The rationale behind this is that the clinical presentation of COVID-19 in children overlaps with other infections. There is no specific clinical, radiological, or laboratory criteria that are good enough to incriminate COVID-19 from other paediatric conditions/infections.
- Therefore, most children infected with COVID-19 require only symptomatic care.

General Care for Child with COVID-19

- 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 (adjust in liver impairment)*
- 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)*
- Nasogastric feeding or intravenous hydration started when child is unable to tolerate oral feeds.
  - *Avoid aggressive fluid management.*
- Avoid use of nebulization. When B2 agonist is needed, deliver through spacer by using metered-dose inhaler (MDI).
- In critical (stage 5) cases, additional pressure and ventilatory support may be required including intubation.

Use of Antibiotics

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

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.
- For pneumonia
- For Sepsis
- Streptococcal/Staphylococcal TOXIC SHOCK SYNDROME

Refer National Antibiotic Guideline 3rd Edition

Use of Steroids

- The use of steroids is not routinely recommended unless for other established indication .

Use of Intravenous Immunoglobulin (IVIG)

- Routine use of IVIG has not been shown to be of any benefit to individual with COVID-19. It can be considered is in Kawasaki-like syndrome or toxic shock syndromes.

Use of Specific Anti-Viral and Immunomodulators Against COVID-19

- There is currently limited evidence of efficacy of antiviral and immune-modulators for COVID-19 in adults and no evidence in children. Use of anti-viral should be considered on a case by case basis (high risk group or overall risk of progression to more severe form) in:
- **Stage 4** where the child exhibit new requirement for supplemental O2 or increase from baseline without new or increased need for ventilatory support (invasive or non-invasive)
- **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.

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 is currently limited evidence of efficacy of antiviral and immune-modulators for COVID-19 in adults and no evidence in children.
- Use of anti-viral should be considered on a case by case basis (high risk group or overall risk of progression to more severe form) in:
  - **Stage 4** where the child exhibit new requirement for supplemental O2 or increase from baseline without new or increased need for ventilatory support (invasive or non-invasive)
  - **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.

The preferred anti-viral agent:

- Remdesivir (not available yet)
- Use of Hydroxychloroquine in the absence of Remdesivir. Even though the data published on human studies are conflicting and hampered by small size and lack of peer review; advantages are, it is an anti-malarial drug used since old days with generally acceptable side-effects.
- For children where use of hydroxychloroquine is contra-indicated (prolonged QTC interval or cardiac disorder with risk of arrythmia); the use of Lopinavir/Ritonavir can be considered.
- 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.

Table 3: Treatment Regime of Anti-viral Agents for Paediatric COVID-19 Cases

Agent	Paediatric dose/duration	Comment
Hydroxychloroquine	Infants and children 6.5mg/kg/dose (max.:400mg) PO 12hourly on D1; followed by 3.25mg/kg/dose (maximum 200mg PO 12hourly on D2-D5.	• Need to do 12 lead ECG to check QTC interval daily • Avoid drug-drug interactions with other agent which can cause prolonged QTC interval (e.g. azithromycin) • Monitor liver functions • Monitor for hemolysis (with G6PD deficient) • Side effects: Rash, Retinopathy, Nausea, Glucose fluctuations, Diarrhea and other GI symptoms. Need written consent.
Remdesivir	Body weight <40kg: 5mg/kg IV loading dose; followed by 2.5mg/kg/dose IV q24h Body weight >40kg: 200mg IV loading dose on D1; followed by 100mg IV q24hr	• Duration:5-10 days (shorter i.e. 5 days for fast responders) • Monitor liver functions • Need adjustment in renal impairment Need written consent.

Table 3: Treatment Regime of Anti-viral Agents for Paediatric COVID-19 Cases (cont…)

Agent	Paediatric dose/duration	Comment
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)	Neonates above 14 days ≥ 42 weeks and children: Lopinavir 300mg/m^2/dose (max 400mg) PO twice a day **a. Syrup formulation** Body weight — Dose 3 – 5kg — 1ml 12hrly 6 – 9kg — 1.5ml 12hrly 10 – 13kg — 2.0ml 12hrly 14 – 19kg — 2.5ml 12hrly 20 – 24kg — 3.0ml 12hrly **b. Tablet (200mg/50mg)** >35kg: 400mg/100mg 12hrly	• 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.

Immune modulators

- 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.
- Children who require any anti-viral or immune modulators need to discuss with paediatric infectious diseases specialists.

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.

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 diseases.
- Report from multicenter panel from Pediatric Infectious Diseases Society of North America and Center of Disease Control suggest that these group of children might have higher risk of mortality or morbidity when they contract this viral illness.
  - Infant < 1 year
  - Severely immunocompromised children (e.g. related to cancer, chemotherapy, radiation therapy, hematopoietic cell/solid organ transplant, high dose glucocorticoids use)
  - Children with significant cardiac disease
  - Children with chronic pulmonary disease (including moderate-severe asthma)
  - Chronic kidney disease undergoing dialysis
  - Chronic liver disease (e.g. chronic hepatitis)
  - Endocrine disorders (e.g. diabetes mellitus)
  - Neurologic or neuromuscular condition

Chiotos K et al. Multicenter initial guidance on use of anti-viral for children with COVID-19/SARS-CoV-2. J Pediatric Infect Dis Soc 2020.

Bialek,S. Morb Mort Wkly Report Mac,2020

New Syndrome of COVID-19

- Recently report from Europe about a small group of children presenting with multisystem inflammatory syndrome resembling other common paediatric inflammatory conditions including Kawasaki Disease (KD)°, Staphylococcal and Streptococcal toxic shock syndromes, bacterial sepsis and macrophage activation syndrome. (Mnemonics-PMIS-TS).

Preliminary Case Definition of Paediatric Multisystem Inflammatory Syndrome (PMIS-TS)

- 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)
- Exclusion of other microbial cause including bacterial sepsis, Staphylococcal or Streptococcal shock syndromes, and infections associated with myocarditis such as enterovirus.
- 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/

Clinical and Laboratory Features of PMIS-TS

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

Discharge Criteria

- A child admitted for COVID-19 can be discharged when there is:
  - *Clinical improvement of symptoms with resolution of fever.*
  - *Evidence of viral clearance from upper respiratory tracts with two-swabs being negative for COVID-19 at least 24 hours apart with at least one sample taken after day 13 of illness.*
  - ***For symptomatic patients** after resolution of symptoms, samples should be collected at least 8 days after the onset or after 3 days without fever.*
  - ***For asymptomatic patients**, the test to document virus clearance should be taken at a minimum of 14 days after the initial positive test.*