

CLINICAL MANAGEMENT OF CONFIRMED COVID-19 CASE IN ADULT AND PAEDIATRIC

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 multiorgan 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. Supplemental oxygen according to SpO₂
- f. 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
- g. 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.
- h. Patients with COVID-19 illness should not be routinely prescribed antibiotics unless suggestive of bacterial illness
- i. Ensure good hydration in children by encouraging their usual milk/diets.

2. Clinical progression of COVID -19

- a. Majority of the patients present with mild disease in clinical category 1 to 3.
- b. In a minority of patients, the disease progresses to a more severe state needing oxygen supplementation and ICU care. This deterioration can be due to the following reasons (etiologies may overlap):

- I. Cytokine Release Syndrome (CRS) which is a systemic inflammatory response associated with rapidly worsening pneumonia with or without multiorgan involvement.
- II. Viral effect of the disease, typically in the first week of illness or can be prolonged if immunomodulators were given too early.
- III. Decompensation/ flare up of underlying comorbid illness
- IV. Complications such as Thromboembolism, Nosocomial pneumonia

3. Specific Treatment

- a. No specific treatment for COVID-19 infection is currently approved.
- b. Data from the RECOVERY trial, a large, randomised controlled trial of possible treatments involving more than 11,000 patients admitted to hospital with COVID-19 has shown that hydroxychloroquine is not an effective treatment in patients hospitalised with COVID-19 and does not reduce mortality.
- c. 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
3	No treatment required. Close observation of vital signs and oxygen saturation especially if patients have the following risk factors <u>If presence of risk factors</u> <ul style="list-style-type: none"> • Age \geq 60 years old • Co-morbids such as hypertension, diabetes, chronic kidney disease, chronic lung disease • Cardiovascular disease • Immune compromised • Obesity

Look out for the following Warning Signs in patients presenting with category 1-3. If patient has more than 1 warning signs, consider treating as category 4 disease.

Warning Signs suggestive of Cytokine Release Syndrome (CRS)*

- a. Clinical
 - Persistent or new onset fever
 - Lethargy

- Respiratory rate more than 25
- Exertional dyspnea
- SpO2 room air <95%

b. Laboratory

- Increasing or raised CRP
- Increasing or raised Ferritin
- Increasing/ raised LDH
- Dropping Absolute lymphocyte count (ALC),

c. 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 may be due to either uncontrolled viral effect, decompensation of underlying comorbidity, thromboembolism or nosocomial infection rather than due to Cytokine Release Syndrome.*

4	<p>A) Antiviral treatment</p> <ul style="list-style-type: none"> • Kaletra (Lopinavir/Ritonavir) 2 tabs bd and • Favipravir 1600mg bd for 1 day then 600mg bd <p>Duration: 5 - 10days</p> <p>(teratogenic; Favipiravir is contraindicated for women of childbearing potential and men whose partner is of childbearing potential/ no data available for use in patients with renal impairment)</p> <ul style="list-style-type: none"> • Consider adding SC interferons Beta 1a 44mcg stat then EOD / Interferon Beta 1b 250mcg stat then EOD (3-5 doses) to the above combination regime in the first week of illness as viral activity may predominate. It may not be useful if started in the second week of illness. <p>B) Immuno-modulatory treatment</p> <p>IF there is disease progression with evidence of Cytokine Release Syndrome, consider adding (needs discussion between ID physician and ICU specialists)</p> <ul style="list-style-type: none"> • IV Dexamethasone 4mg bd or tds : 3 - 5 days OR • IV Methylprednisolone 1-2mg/kg daily : 3- 5 days OR • IV Tocilizumab 8mg/kg single dose – <i>preferred in late presentation</i>
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	<p>c) Thrombo-embolism treatment</p> <p>Refer to section <i>Prophylaxis therapy against VTE</i> Check medication list for possible drug-drug interactions (https://www.covid19-druginteractions.org/)</p>
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 Patient¹	LMWH Enoxaparin 0.5mg/kg daily	SC UFH 5000u bd to tds
High Risk Patient² 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

¹ Higher doses to be considered in patients more than 100kg

² 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 hypoxemia, 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 at first presentation
2	SYMPTOMATIC WITHOUT PNEUMONIA	Vitals signs monitoring 8-12hrly Doctors review bd	FBC/RP/LFT/CRP/RBS (or capillary blood sugar) at baseline FBC/CRP biweekly Rest, repeat as indicated If patient has risk factors, repeat bloods (FBC, CRP) daily during the critical phase - D5-10 of illness CXR at first presentation Repeat as indicated Baseline ECG for those with risk factors, repeat as necessary If patient shows any warning signs (see below), repeat CXR and bloods immediately

Annex 2e

3.	PNEUMONIA NOT REQUIRING OXYGEN	<p>Monitoring as per category 2, however in the presence of Risk Factors vital signs monitoring 6-8hrly</p> <p>If further clinical deterioration, increase frequency of monitoring</p> <p>Doctors review TDS</p>	<p>FBC/ RP/LFT/CRP/RBS (or capillary blood sugar) at baseline</p> <p>If any warning signs – repeat daily (FBC, CRP, Ferritin/LDH)</p> <p>Baseline ECG for those with risk factors. Repeat as necessary</p> <p>CXR at first presentation. Repeat CXR if patient develops warning signs</p>
4.	PNEUMONIA REQUIRING OXYGEN	<p>Refer ICU</p> <p>Vitals signs monitoring 4hrly</p> <p>Doctors to review 4hrly until admission into ICU</p>	<p>Daily FBC/ RP/LFT/CRP and Ferritin/LDH Procalcitonin*</p> <p>CXR at first presentation Repeat CXR if further deterioration</p> <p>Baseline ECG. Repeat as necessary</p> <p><i>*Procalcitonin can be raised in both bacterial infection and CRS</i></p>
5.	CRITICALLY ILL PATIENT	<i>As per local standardized ICU monitoring protocol</i>	

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

Criteria for assessing the disease severity was already proposed in previous guideline where different stages have been applied to help in managing a confirmed case. 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 below).

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

Clinical stage			
1	Mild Disease	Asymptomatic	<ul style="list-style-type: none"> Only RT-PCR test positive
2		Symptomatic, No pneumonia	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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)

Annex 2e

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)	<ul style="list-style-type: none"> • 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
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: <ul style="list-style-type: none"> • 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) 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.

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. For children with high risk of disease progression, need to obtain baseline CRP, D-dimer, ferritin, lactate dehydrogenase (LDH) and monitor them (2-3 times per week) if there is concern for worsening disease.

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

DIAGNOSTIC TESTS	
HEMATOLOGY/ BIOCHEMISTRY	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • SARI panel (21 pathogens are currently detected including Influenza, Mycoplasma, AdenoV and Enterovirus)
MICROBIOLOGY	<ul style="list-style-type: none"> • Blood Culture & Sensitivity • Urine Culture & Sensitivity • CSF Culture & Sensitivity (when indicated)

	<ul style="list-style-type: none"> • HIV test (if considering Lopinavir/Ritonavir)
RADIOLOGY	<ul style="list-style-type: none"> • Chest X-ray (or Ultrasound of Thorax) • Echocardiogram (heart involvement/ KD)
OTHERS	<ul style="list-style-type: none"> • 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.

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 confirms 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 Amoxicillin 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. Hence steroids, can be use in these situations (extrapolated from adults)

- 1) Children with **COVID-19 Stage 4 or 5** who does not respond to the initial supportive therapy (Need to discuss with Paediatric Infectious Disease Specialist).
- 2) Underlying medical conditions where steroid is needed (e.g.; bronchial asthma, relapse nephrotic syndrome etc.)
- 3) An additional diagnosis where steroid therapy is appropriate.

Preferred Drug	Dose
Dexamethasone (IV or oral)	0.15mg/kg/dose once daily (max: 6mg)
Alternative Drug	Dose
Hydrocortisone	0.5mg/kg/dose 12 hourly x 3-7days

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 syndrome or toxic shock syndromes.

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 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:

- a. **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)

- 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, but most trial recruiting cases currently do not even include children below 12 years of age even in United States. 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 other agent that could be considered is 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.
- c. For children where use of hydroxychloroquine is contra-indicated (prolonged QTC interval or cardiac disorder with risk of arrhythmia); 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.⁶

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

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.	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Duration:5-10 days (shorter i.e. 5 days for fast responders) • Monitor liver functions • Need adjustment in renal impairment Need written consent.												
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)	<p>Neonates above 14 days \geq 42 weeks and children:</p> <p>Lopinavir 300mg/m² /dose (max 400mg) PO twice a day</p> <p>a. Syrup formulation:</p> <table border="1"> <thead> <tr> <th>Body weight</th> <th>Dose</th> </tr> </thead> <tbody> <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> </tbody> </table> <p>b. Tablet (200mg/50mg) >35kg: 400mg/100mg12hrly</p>	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	<ul style="list-style-type: none"> • Duration:7-14 days • Not recommended with ribavirin • Side effects: Hepatotoxicity, pancreatitis, glucose intolerance, OT prolongation, lipid elevation and fat redistribution • Check HIV status prior to commencement. • Drug-drug interaction via cytochrome P450 Need written consent.
Body weight	Dose													
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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.

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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Need to discuss with paediatric infectious disease consultant Side effects: GI perforation, Anemia, Hepatitis, Infusion related risk, risk of secondary infection.

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 these group of children might have higher risk of mortality or morbidity when they contract this viral illness. ⁶ Center of Disease Control also provides information about underlying medical conditions according to age. 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. This high-risk group is: ^{6,7,10}.

- Infant < 1 year (especially < 1month)
- 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 ^a (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 conditions
- Any medical conditions

4.1 New Syndrome of COVID-19

Recently paediatrician from Europe reported a small group of children presenting with multisystem inflammatory syndrome resembling other common paediatric inflammatory conditions including Kawasaki Disease (KD)⁶, Staphylococcal and Streptococcal toxic shock syndromes, bacterial sepsis and macrophage activation syndrome. (Mnemonics-PMIS-TS).

European Center of Disease Prevention and Control (ECDC) reported a total of ≈230 suspected cases of this new syndrome including two deaths, one each in UK and France. These cases are currently being further investigated. Prior to this, epidemiological studies have shown that children in Europe appear to be less affected by COVID-19 like their counterparts in China. Only 2.1% of all laboratory-confirmed COVID-19 cases reported to The European Surveillance System (TESSy) were in the age group between 0 and 14 years of age.

To date, an association between SARS-CoV-2 infection and this new clinical entity of multisystem inflammation has not yet been established, although an association appears plausible. 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.

Preliminary 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.⁷This 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 paediatric 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 aspirin
- b. For Toxic shock syndrome: IVIG as an adjunct; 1g/kg on D1, followed by 0.5mg/kg on 1-2 subsequent days.

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

Fever lasting at least 5 days
At least 4 out of the 5 of the following: <ul style="list-style-type: none"> • Bilateral non-purulent conjunctivitis • Mucosal changes of the oropharynx (injected pharynx, 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 <i>Adapted from Paediatric protocols for Malaysian Hospital, 4th edition.</i>

Table 5: Clinical and laboratory features of PMID-KS

Clinical	Laboratory
<p>All:</p> <ul style="list-style-type: none"> Persistent fever with temperature >38.5°C <p>Most:</p> <ul style="list-style-type: none"> Oxygen requirement Hypotension <p>Some:</p> <ul style="list-style-type: none"> Abdominal pain Confusion Conjunctivitis Cough Diarrhoea Headache Lymphadenopathy Mucus membrane changes Neck swelling Rash Respiratory symptoms Sore throat Swollen hands and feet Syncope Vomiting 	<p>All:</p> <ul style="list-style-type: none"> 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) <p>Some:</p> <ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> 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:

- For **symptomatic patients** after resolution of symptoms (at least 3 days without fever) **AND** improvement in respiratory symptoms **AND** at least 14 days have passed since symptoms first appeared.
- For **asymptomatic patients** 14 days have passed since the date of their first positive diagnostic test.
- 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.

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