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

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

Confirmed COVID-19 patients are classified into 5 categories as stated in Table 1. The clinical management of the patient is based on these categories.

Table 1: Clinical Staging of COVID-19

Clinical Stage	Disease Severity
1	Asymptomatic
2	Symptomatic, No Pneumonia
3	Symptomatic, Pneumonia
4	Symptomatic, Pneumonia, Requiring supplemental oxygen*
5	Critically ill with or without other organ failures

**In patients who present with hypoxia, it is important to determine if the cause is due to COVID-19 pneumonia or other causes (e.g. bronchial asthma, fluid overload and heart failure). Positive SST does not necessarily categorize the patients as category 4.*

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.
c. Patients admitted with COVID-19 illness should have regular blood investigations and imaging as recommended.
d. For patients who need bronchodilator therapy e.g. salbutamol; avoid using nebulizer. Instead, use MDI with a spacer.
e. In patients with COVID-19 who require supplemental oxygen, a trial of self-proning is recommended, if the patient can tolerate. 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 infection.

2. Clinical progression of COVID-19

a. Majority of the patients present with mild disease in clinical category 1 to 2.
b. Patients with age >50 years and those with chronic comorbid illnesses especially in the unvaccinated population have higher risk of developing more severe disease. Risk factors associated with severe disease are shown in Table 2. Warning signs and predictors for progression to severe disease are shown in Table 3.
c. Among vaccinated patients, infection due to omicron variant may present with less clinical deterioration. Hence, patients with hypoxia will need careful assessment before initiating steroid therapy.
d. In patients with risk factors, worsening respiratory symptoms may still develop and thus need to be monitored closely. The 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

Table 2: Risk Factors Associated with Severe COVID-19 Disease.

2A. Supported by meta-analysis/ systematic review	
• Not fully vaccinated • Age >50 years (risk increases with each decade) • Cancer • Cerebrovascular disease • Chronic kidney disease • Chronic liver disease • COPD, chronic lung diseases • Diabetes mellitus, type 1 and type 2	• HIV • Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies) • Obesity (BMI>30kg/m^2) • Pregnancy and Recent Pregnancy • Primary Immunodeficiencies • Smoking, current and former • Solid organ or blood stem cell transplantation
2B. Supported by other evidence	
• Asthma • Hepatitis B and C • Hypertension • Overweight (BMI>25kg/m^2)	• Sickle cell disease • Substance use disorders • Thalassemia

For complete list, please refer to https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html

Table 3: Warning Signs that Predict Deterioration.

Clinical	Laboratory	Radiological

• Persistent fever >2 days
• Persistent symptoms - lethargy/ vomiting/ diarrhea
• Worsening cough/ breathlessness
• Reduced level of consciousness in the absence of alternate explanations such as hypoglycemia, uraemia etc.
• Respiratory compromise
  ○ Exertional dyspnoea / desaturation
  ○ Respiratory rate more than 25
  ○ Spo2 <95% or a 3% drop in SST
	• A rising CRP value or a single CRP value of ≥50mg/l*
	• A rising ferritin level or a single value > 500
	• A raised LDH
	• Neutrophil lymphocyte ratio ≥ 3.13
		Features of severe pneumonia, multi-lobular involvement, or rapidly worsening chest X-ray

Note: The presence of warning signs should prompt for close monitoring of patients (Refer Table 7)

**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 viral pneumonia, decompensation of underlying comorbidity, thromboembolism or other concomitant infection rather than due to inflammation.*

3. Specific Treatment

a. The treatment regimen suggested below is likely to change as new evidence emerges. (Table 6)
b. The initiation of oral antiviral therapy in mild disease (Category 2-3) is based on Eligibility Criteria as stated in Table 4 and who are not in the non-indication / contraindication criteria as below.

Non- Indication / Contraindication Criteria

1. Age < 18 years old
2. Symptoms onset > 5 days
3. Patient requires oxygen
4. Pregnant/breastfeeding
5. Drug to drug interaction (refer to https://www.covid19-druginteractions.org/checker)
6. Severe renal disease
7. Severe liver disease

Table 4: Eligibility Criteria for Antiviral Therapy (Category 2-3).

ELIGIBILITY CRITERIA	YES	NO
1. Age ≥ 60 years old		
2. Immunocompromised		
3. Any co-morbidiy		
4. Obesity		
5. Current or ex-smoker		
6. Unvaccinated or Incomplete vaccination		

Patients with **ANY** of the above criteria will be eligible for oral antiviral therapy

Table 5: Immunocompromised Conditions

- Patients who are within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Bone marrow transplant / Solid organ transplant on immunosuppressive therapy
- Patients with hematologic malignancies/ cancer who are on active chemotherapy
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm
- Chronic lymphocytic leukaemia and multiple myeloma with hypogammaglobulinemia

Table 6: Specific Treatment of COVID-19 Disease

Category	Recommended	Alternative	Remarks
Category 1	No treatment required Monitor for warning sign		
Category 2 Category 3	For high risk patients (score ≥3 in Table 4) AND within 5 days of illness: 1. Nirmatrelvir 300mg with Ritonavir 100 mg (taken together) BD for 5 days[1] *(Preferred)* OR 2. Molnupiravir 800mg BD for 5 days[2] *(If contraindicated to Nirmatrelvir or Ritonavir)* ---------- In category 3, prophylactic dose of heparin[3] • In hospitalised patient • LMWH or UFH (LMWH is preferred) • Check contraindication	For high risk patients (score ≥3 in Table 4) AND within 5 days of illness: IV Remdesivir* 200mg loading (D1), then 100mg daily (D2-D3)[4] *(Only if Nirmatrelvir/Ritonavir and Molnupiravir are not available)* OR Casirivimab 600mg/ Imdevimab 600mg (Ronapreve)[5] • Not for Omicron variant • IV or SC single dose	Corticosteroid is not recommended in non-hypoxic cases unless for other indications. Nirmatrelvir/Ritonavir (Paxlovid) • Renal adjustment: eGFR 30-60 mL/min: Nirmatrelvir 150mg with Ritonavir 100mg BD, <30 mL/min: not recommended • No data in pregnancy and breastfeeding mother • Review concomitant medications to avoid drug-drug interaction due to Ritonavir (potent CYP3A4 inhibitor). Please refer to the list of common drug interactions (Appendix 1), or visit https://www.covid19-druginteractions.org/checker Molnupiravir • Not recommended in pregnancy and breastfeeding mother • Females of childbearing potential should use reliable contraception during treatment and for 4 days after the last dose Remdesivir • Not recommended for eGFR < 30 ml/min • Liver function testing before and during therapy • No data in pregnancy and breastfeeding mother *Currently not registered for this indication under NPRA

Category	Recommended	Alternative	Remarks
Category 4a - requiring nasal prong or face mask #	IV Dexamethasone phosphate[6] 8mg od (12mg if BMI >30) for up to 10 days or until discharge AND Anticoagulation therapy • Therapeutic heparin is recommended[7] (preferably when D-dimer >ULN) • Otherwise, for prophylactic heparin • LMWH or UFH (LMWH is preferred) • Check for bleeding risk and contraindication	Dexamethasone AND IV Remdesivir 200 mg loading (D1), then 100 mg daily (D2-D5)[8] --- For patients on dexamethasone with increasing oxygen needs and systemic inflammation, consider • IV Dexamethasone phosphate 24mg od[9] • Dexamethasone and Baricitinib • IV Methylprednisolone[10] 2mg/kg for 3-5 days*	Remdesivir • Maximum benefit if started ≤ 10 days of illness. • Is not recommended for eGFR < 30 ml/min *There is currently insufficient evidence to recommend for or against a short course of methylprednisolone as escalation treatment. If corticosteroid is contraindicated, can use Remdesivir AND Baricitinib Note: IV dexamethasone phosphate 8mg = IV dexamethasone base 6mg = oral dexamethasone 6mg. Step-down to oral dexamethasone 6mg once improved

 # Note: In patients who present with hypoxia, it is important to determine if the cause is due to COVID-19 pneumonia or other causes (e.g. bronchial asthma, fluid overload and heart failure). Positive SST does not necessarily categorize the patients as category 4.

Category	Recommended	Alternative	Remarks
Category 4b - requiring high flow mask OR Category 5a - non-invasive ventilation (NIV), including HFNC	IV Dexamethasone phosphate 24mg od for 5 days, then 12mg od for 5 days[11] AND Prophylactic dose of heparin • LMWH or UFH (LMWH is preferred) • Check contraindication • If patient is started on therapeutic dose earlier, switch to prophylactic dose	Dexamethasone AND IV Remdesivir 200 mg loading (D1) and 100 mg daily (D2-D5) OR IV Methylprednisolone 2mg/kg/day for 3-5 days, then step down to IV Dexamethasone phosphate 8-12mg od once improved ---------- Within 14 days of illness and with increasing oxygen needs and systemic inflammation, consider: Corticosteroid AND Tocilizumab[12] OR Corticosteroid AND Baricitinib[13] OR IV Remdesivir 200 mg loading (D1) and 100 mg daily (D2-D5) AND Baricitinib	Remdesivir • Maximum benefit if started ≤ 10 days of illness. • Is not recommended for eGFR < 30 ml/min Tocilizumab: • IV 8mg/kg single dose (max: 800 mg/dose) • Tocilizumab is preferred over Baricitinib in patients with poor gut absorption and eGFR<15ml/min Baricitinib: • 4mg OD oral x 14 days or until hospital discharge (whichever earlier) • Avoid in patients with previous history of thrombosis • Renal adjustment: eGFR ≥60: 4mg OD, 30-59: 2mg OD, 15-29: 1mg OD, <15: not recommended Note: IV Dexamethasone phosphate 24mg = IV Dexamethasone base 20mg
Category 5b - mechanical ventilation with or without other organ failures	IV Dexamethasone phosphate 24mg od for 5 days, then 12mg od for 5 days AND Prophylactic dose of heparin • LMWH or UFH (LMWH is preferred) • Check contraindication • If patient is started on therapeutic dose earlier, switch to prophylactic dose	IV Methylprednisolone 2mg/kg/day for 3-5 days, then step down to IV Dexamethasone phosphate 8-12mg od once improved OR Corticosteroid AND Tocilizumab OR Corticosteroid AND Baricitinib	Remdesivir is not recommended Tocilizumab (as above) Baricitinib (as above)

4. Pre-exposure prophylaxis (PrEP) for COVID-19

Tixagevimab plus Cilgavimab (EVUSHELD)[14] can be used as PrEP for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have COVID-19 infection, who have not been recently exposed to an individual with COVID-19 infection, AND who:

- Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination; OR
- Are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe adverse reactions to a COVID-19 vaccine or any of its components.

Tixagevimab 300mg plus Cilgavimab 300mg[15] are administered as two separate consecutive intramuscular injections. Study showed that EVUSHELD may be effective for 6 months post administration. There are no safety and efficacy data available with repeat dosing. EVUSHELD should be given at least 2 weeks apart from COVID-19 vaccination (immunocompromised patients).

Due to restricted availability of EVUSHELD, it shall be given to patients with severe immunocompromised conditions (as listed in Table 5).

5. COVID-19 Treatment in Pregnancy

In general, the therapeutic management of pregnant patients with COVID-19 should be the same as for non-pregnant patients. Pregnant patients should be counselled about the increased risk for severe disease from COVID-19 infection. Treatment for COVID-19 in pregnant or lactating individuals should not be withheld because of theoretical safety concerns[16].

Clinician should discuss with patients regarding the use of investigational drugs or drugs that are approved for other indications as treatments for COVID-19. During this shared decision-making process, the patient and the clinician should consider the safety of the medication for the pregnant or lactating individual and the fetus and the severity of maternal disease.

All pregnant women should be assessed for risk of VTE and prescribed thromboprophylaxis with LMWH unless there is a contraindication. In unwell mothers, chest X-Ray should be performed when indicated, and not delayed because of concerns of possible maternal and fetal exposure to radiation, as maternal wellbeing is paramount.

In pregnant or postpartum women (up to 6 weeks) who require supplemental oxygen due to COVID-19 infection, corticosteroid therapy should be given for 10 days or up to discharge, whichever is sooner[17, 18].

- If steroids are not indicated for fetal lung maturity, oral prednisolone 40 mg once a day, or IV hydrocortisone 80 mg twice daily, for 10 days or until discharge, whichever is sooner.
- If steroids are indicated for fetal lung maturity, IM Dexamethasone phosphate 6mg 12 hourly x 2 days, followed by oral prednisolone 40 mg once a day, or IV

hydrocortisone 80 mg twice daily, to complete a total of 10 days or until discharge, whichever is sooner.

- In more severe disease, to follow treatment in Table 6.

Table 7: Clinical Monitoring in Hospital Settings

Note: For monitoring in primary care setting, please refer to the respective protocol in separate document.

Clinical Stage		Clinical monitoring	Laboratory and Radiological Monitoring
1.	**Asymptomatic**	Vitals signs monitoring once a day Doctors review once a day	Blood tests and CXR are not necessary unless indicated (e.g. presence of warning signs)
2.	**Symptomatic without pneumonia**	Vitals signs monitoring once a day Doctors review once a day However, in the presence of warning signs: • Vital signs monitoring 2-3 times per day • SST test at each monitoring	FBC, RP, LFT, CRP, RBS (or capillary blood sugar) at baseline CXR at first presentation. Baseline ECG for those with risk factors, repeat as necessary If any warning signs: • Repeat stat and as necessary (FBC, CRP, LDH, Ferritin) • For other tests, repeat as indicated • Repeat CXR if patient develops warning signs
3.	**Pneumonia not requiring oxygen**	Vitals signs monitoring once a day Doctors review once a day However, in the presence of warning signs: • Vital signs monitoring 2-3 times per day • SST test at each monitoring	FBC, RP, LFT, CRP, RBS (or capillary blood sugar) at baseline CXR at first presentation Baseline ECG for those with risk factors, repeat as necessary If any warning signs: • Repeat stat and as necessary (FBC, CRP, LDH, Ferritin) • For other tests, repeat as indicated • Repeat CXR if patient develops warning signs
4.	**Pneumonia requiring oxygen**	Refer ICU as necessary Vitals signs monitoring 4hrly Doctors to review every 4-6 hours	FBC, RP, LFT, CRP, LDH, Ferritin, 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*

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Appendix 1

Common Drug Interaction with Nirmatrelvir/Ritonavir (Paxlovid)

Drug Class	Drug	Remarks
Anticonvulsants	Carbamazepine, Phenobarbital, Phenytoin	Significantly reduced PAXLOVID plasma concentration maybe associated with the potential loss of virologic response and possible resistance.
Antifungals	Voriconazole	Decrease the level or effect of Voriconazole. Avoid or use an alternative drug.
Anticoagulants	Warfarin Rivaroxaban	INR may increase or decrease. Close monitor INR. Increased bleeding risk with Rivaroxaban. Avoid concomitant use.
Antigout	Colchicine	Co-administration is contraindicated due to the potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Anti-HIV protease inhibitors	Atazanavir, Darunavir	Monitor for increased PAXLOVID or protease inhibitor adverse events with concomitant use.
Antimycobacterial	Rifampicin	Decrease the level of PAXLOVID. Co-administration is contraindicated due to potential loss of virologic response and possible resistance.
Antipsychotics	Quetiapine	If co-administration is necessary, reduce the Quetiapine dose and monitor for quetiapine-associated adverse reactions.
Calcium channel blockers	Amlodipine, Felodipine, Diltiazem, Nifedipine	A dose reduction may be needed for these drugs when co-administered with PAXLOVID.
Cardiac glycosides	Digoxin	Increase the level of Digoxin. Close monitoring of serum Digoxin levels during co-administration.
HMG-CoA reductase inhibitors	Lovastatin, Simvastatin, Atorvastatin, Rosuvastatin	Increase the level of HMG-CoA reductase inhibitors. Co-administration is contraindicated due to the potential for myopathy including rhabdomyolysis (Lovastatin/Simvastatin). Discontinue the use of these statins while on PAXLOVID.

Hormonal contraceptive	Ethinyl estradiol	An additional, non-hormonal method of contraception should be considered.
Immunosuppressants	Cyclosporin, Tacrolimus, Sirolimus	Increase level of Immunosuppressant. Therapeutic concentration monitoring is recommended for immunosuppressants. Avoid the use of PAXLOVID when close monitoring of immunosuppressant serum concentrations is not feasible. Avoid concomitant use of Sirolimus and PAXLOVID.
Long-acting beta-adrenoceptor agonist	Salmeterol	The combination may result in an increased risk of cardiovascular adverse events associated with Salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Narcotic analgesics	Methadone	Decrease the level of Methadone. Monitor patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
PDE5 inhibitor	Sildenafil for PAH	Increase the level of sildenafil. Co-administration is contraindicated due to the potential for sildenafil-associated adverse events including visual abnormalities hypotension, prolonged erection and syncope.
Systemic corticosteroids	Dexamethasone, Methylprednisolone	Increased risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids such as prednisolone should be considered.

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 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

5	Critical Illness	Critically ill with or without other organ failures 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:** currently licensed by most authority for use in children ≥ 12 years old and weighing at least 40kg with severe symptoms (pneumonia and require supplemental oxygen). While evidence for this anti-viral is limited, Remdesivir had been used in children of all ages, and can be considered on a case-by-case basis in consultation with Paediatric Infectious Diseases experts.
b. The use of Lopinavir/Ritonavir can be considered when Remdesivir is 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)

Agent	Paediatric Dose/Duration	Comment
Remdesivir	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	• Duration: 5-10 days (shorter i.e. 5 days for fast responders) • Side effect: Nausea, ALT and AST elevations, Increase in prothrombin time, Hypersensitivity reactions, • Monitor liver functions: To discontinue if ALT> 10 x of upper limit of normal or increased ALT with signs and

<table>
<tr>
<td></td>
<td></td>
<td>symptoms of liver inflammation are observed.
• 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, OT 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, IL-1 among others. Hence the use of immune modulators as adjunct therapy in certain circumstances where this phenomenon is suspected. The evidence for this is derived from other hyper inflammatory conditions seen in children including Macrophage Activation syndrome (MAS) and Haemophagocytic Lymphohistiocytosis (HLH). Just like use of anti-viral, the risk against benefit needs 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)

Glucocorticoids are a readily available and inexpensive option for immunomodulation. In paediatric patients with severe COVID-19 and hyper inflammation who have refractory disease despite glucocorticoid administration, biologics could be considered for treatment.

There are two treatment options: Tocilizumab (Blockade of IL-6 receptor) or Anakinra (Blockade of IL-1 receptor).

Despite being generally well tolerated, both Tocilizumab and Anakinra carry a risk for infection. Thus, it is imperative to carefully evaluate the risk of co-infection, as co-infection especially in the context of SARS-CoV-2 is a risk factor for poor outcomes.

Of the two, some experts prefer Anakinra since its relatively safe in severe infections, including sepsis.[15] It also has a short half-life, so can be discontinued rapidly if not effective or if there are side effects.

In immunocompromised patients, these immunomodulators agents should be used with caution. Therefore, decisions about the use of immunomodulator agents should be made on a case-by-case basis according to disease severity and in consultation with Paediatric Infectious Disease Specialist/Consultant.

The use of biologic therapy as an additional immunomodulator should only be considered in patients refractory to corticosteroid and IVIG treatment or those with severe, life-threatening MIS-C manifestations.

a) Tocilizumab

Use of this agent should be avoided in children with:

- Known hypersensitivity to Tocilizumab
- Uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral infections
- Absolute neutrophil count (ANC) <1000 cells/μL
- Platelet counts <50,000/μL
- Alanine aminotransferase (ALT) >5 times the upper limit of normal
- Elevated risk for gastrointestinal perforation

Use of this should be avoided in individuals who are significantly immunosuppressed.

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.

b. Anakinra

Agent	Formulation	Dose	Duration	Indication
Anakinra	subcutaneous	2mg/kg/dose once daily (max 100mg/dose)	5 days	• Moderate disease • Need to discuss with Paediatric Infectious Disease Consultant
	Subcutaneous ** In certain condition, the use of IV formulation can be considered (off label). Need to discuss with experts (Infectious disease/pharmacist /rheumatologist)	2mg/kg/dose (max 100mg/dose)	every 6 hours Day 1, every 8 hours Day2, every 12 hours Day 3, every 24hours Day 4-5.	• Severe disease/shock • Need to discuss with paediatric infectious disease consultant • Side effects: Nausea, Diarhoea, Neutropenia 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.
    - As with adults, children with obesity, diabetes, moderate to severe asthma, chronic lung disease, sickle cell disease are likely at increased risk for developing severe COVID-19.

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 PIMS-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 post infectious 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 (PIMS-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 Paediatric Multisystem Inflammatory Syndrome

Clinical	**Laboratory**
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	**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 ward/isolation facilities.

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

a. For **asymptomatic patients**, may be discharged when medical practitioner deems fit **at any time** to complete **10** days of quarantine at home, after the date of their first positive test either RT-PCR test or RTK antigen for SARS-CoV-2.

b. For immunocompromised hosts, decision to release them from COVID-19 pathway should be taken on case to case basis.
c. For **symptomatic patients,** at least **10-14** days (according to category) have passed since symptom onset **AND** at least 48 hours have passed since resolution of fever without the use of fever-reducing medications **AND** other symptoms such as dyspnoea, cough have improved.

Category	Discharge criteria
2	• Child can be discharged earlier **(<day 7** of quarantine) to continue quarantine at home to complete **10** days (taken from day 1 of symptom): o No longer requires close monitoring and medical intervention o (i.e. Intravenous therapy, frequent bronchodilators) o afebrile for 48 hours prior to discharge o if child is well/symptoms improved AND medical practitioner deems fit
3	• Child can be discharged earlier **(< day 10** of quarantine) to continue quarantine at home to complete **10** days (taken from day 1 of symptom): o No longer requires close monitoring and medical intervention o (i.e. Intravenous therapy, oxygen requirement, frequent bronchodilators) o afebrile for 48 hours prior to discharge o if child is well/symptoms improved AND medical practitioner deems fit
4	• Child can be discharged earlier (**> day 10** of quarantine) to continue quarantine at home to complete **14** days (taken from day 1 of symptom): o No longer requires close monitoring and medical intervention o (i.e. Intravenous therapy, oxygen requirement, frequent o Bronchodilators, intravenous antibiotic therapy) o off oxygen for at least **48hours** o afebrile for 48 hours prior to discharge o if child is well/symptoms improved AND medical practitioner deems fit
5	• **Completed at least 14 days of quarantine** (taken from day 1 of symptom): o No longer requires close monitoring and medical intervention o (i.e. Intravenous therapy, oxygen requirement, frequent o Bronchodilators, intravenous antibiotic therapy, VTE prophylaxis) o off oxygen for at least **72 hours** o afebrile for 48 hours prior to discharge o if child is well/symptoms resolved AND medical practitioner deems fit

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.

6. Children at higher risk for severe COVID-19

Current evidence on which underlying medical conditions in children are associated with increased risk is limited. Evidence suggest children with, medically complex disease including genetic, neurologic, cardiac, haematologic, and metabolic conditions are at higher risk of severe COVID-19. As with adults, children with obesity, diabetes, moderate to severe asthma, chronic lung disease, sickle cell disease, and immunosuppression are likely at increased risk for developing severe COVID-19. Despite their increased risk, most children will have mild disease.

These are NOT considered as comorbidities:

- G6PD deficiency
- Autism
- ADHD
- Slow learner
- Epilepsy
- Stable congenital heart disease: VSD or ASD not in failure, fully corrected heart lesion; e.g. TAPVD post repair not in failure
- Children on aspirin
- Ex-prematurity alone with no other complications like BPD etc.
- Hypertension alone
- Thalassemia trait
- Intermittent bronchial asthma

7. Home monitoring

Refer to Annex 2m - Guideline on Home Monitoring & Management of Confirmed COVID-19 Case at COVID-19 Assessment Centre (CAC) in Primary Care.

8. Referral to Hospital

Refer to Annex 2m - Guideline on Home Monitoring & Management of Confirmed COVID-19 Case at COVID-19 Assessment Centre (CAC) in Primary Care.

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