Management Principles of COVID 19 in Adolescents & Children

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There are two phases of COVID 19 in adolescents (Mangement & Physiology matches adults) namely viremia and immune response . Anti viral drugs have limited role as deterioration in COVID 19 patient is due to hyperinflammatory immune phase of disease . Cytokine release leads to inflammation of endothelium of pulmonary vessels and pulmonary epithelium . During initial pulmonary phase anti thrombotic agents, steroids and anti cytokine drugs will help. Early aggressive treatment can prevent the progression to classical ARDS . Once classical ARDS has developed no therapy works. Clinical, inflammatory, coagulant markers to be followed simultaneously. Clinical examination alone can be deceptive in moderate cases. Most important period is recognition of early pulmonary phase and prompt treatment with steroids. Before discharge there shouldn't be significant drop in saturation after routine work like one minute walk

Key words *– Cytokine storm (CS), macrophage activation syndrome (MAS),hemophagocytic lymphohistiocytosis (HLH), Multisystem inflammatory syndrome in children (MIS-C)*

BASIS OF TREATMENT (PATHOPHYSIOLOGICAL BASIS)

Whenever someone is exposed to a significant viral load and gets infected, further course will depend on immunity, viral load, age of the patient, comorbidities (hypertension, uncontrolled diabetes, immunity, heart ailment, pulmonary ailment, dementia etc). It takes around 3 days after getting the infection (after contact), for a person to become infectious and start spreading the disease. On an average, 6.4 days (2.1-11.1 days) after getting the infection a person can start having symptoms (1) . For treatment point of view disease can be divided into two phases **Fig. 1 , 2**

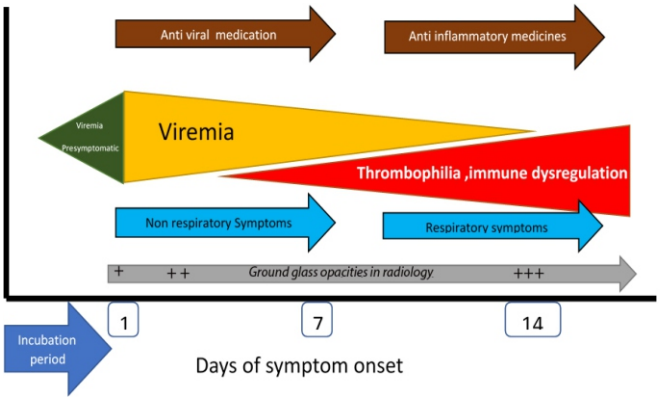


Fig.1 *Pathophysiology of COVID 19. Depicting various stages of disease progression and treatment modalities used.*

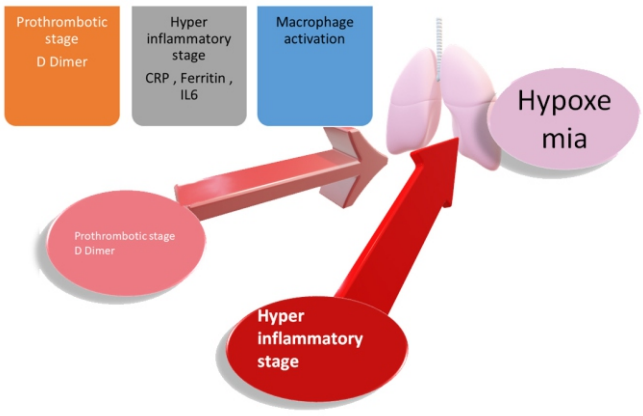


Fig. 2 *Relationship between hyper coagulant , hyperinflammatory and lung hypoxemia*

1) **Symptomatic non pulmonary phase** – Cold, cough , fever , malaise , throat pain , myalgia and loose motions are common symptoms . Following these symptoms patient recovers over next 5 to 7 days . Some patients can remain totally asymptomatic throughout the disease process . 85 percent of patients recover from this stage only due to innate immunity (1). Pathologically in this stage there is predominantly viremia . This is the stage when antiviral therapy like anti viral drugs and antibody therapy can work .

2) **Symptomatic Pulmonary phase** - Clinically this is marked by respiratory symptoms like fast breathing and drop in saturation below or equal to 94%. Two pathological processes can lead to this phase, pulmonary thrombosis and immune dysregulation. Immune dysregulation can manifest as cytokine storm, macrophage activation syndrome. Pulmonary phase can be divided in two parts – early and late (2). Early is "L" type where elastase is low and invasive ventilation should be avoided as much as possible .At this stage anti inflammatory and anti thrombotic therapy plays a major role . If disease progresses this can lead to late pulmonary phase "H" type , with high elastase and behaves like classical ARDS .

Peculiarity of SARS Cov2 is that there is insufficient type I interferon response(too little and too late), paralleled by an aberrant pro-inflammatory chemokine secretion especially IL6 (3). This insufficient interferon beta response point towards the fact that the severity of disease might be due to immune dysregulation, rather than to the level of viremia.IL-6 plays a key role in the pathogenesis of the cytokine storm owing to its pleiotropic properties. Several studies showed that the serum levels of IL-6 are increased in COVID-19 patients and that its circulating levels are positively related to disease severity(3).

CLINICAL MANAGEMENT

STEP I : Classify the patients based on clinical spectrum and investigations

STEP II : Identify patients with co morbid conditions like diabetes, obesity with BMI >25, immunocompromised status, cardiovascular, pulmonary , hepatic , renal, hematologic and neurologic conditions.

STEP III : Risk stratification. Following are considered as high risk cases:

Age <1year , Age >60 year

Clinical features: Fever more than 102 degree fahrenheit persisting after 7 days of onset of symptoms, biphasic fever with second spike, fever with chills and rigor, respiratory symptoms (high RR than physiological rate), pulse oximetry reading less than or equal to 94 percent or drop in SpO_2 more than 4 after 6 minute walk or one minute stand and sit exercise . Persistent tachycardia as per age (more than 110 /min in adult) (3)

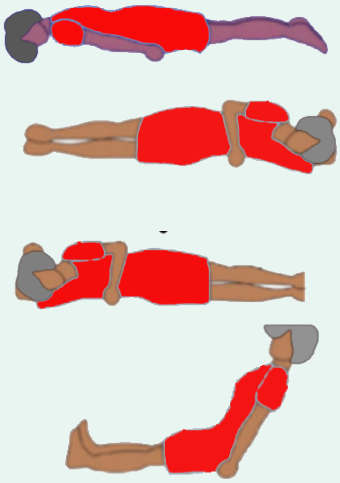
STEP IV : There are three types of patients – Already having baseline tests done within 3 days of presentation , second group are those who presenting for the first time and third group are those who have self-medicated or taken steroids under supervision.

- Baseline investigations (in high risk patients)-Complete blood counts, total leucocyte counts, differential leucocyte counts, C reactive protein, glycosylated hemoglobin, kidney function test, liver function test, troponin I, Thyroid function test, D dimer, LDH, ferritin, blood group.
  - Optional – Blood culture , CPK , IL6 , Pro BNP, Dengue NS1antigen
- Repeat test (in high risk patients or developing high risk features) (4)
  - Daily CBC with DLC, absolute lymphocyte count, LFT, BUN, Cr , Na, K , LDH.
  - Every 3rd day - CRP, D dimer, Ferritin. Frequency and type of tests are decided by clinical condition and disease course . CRP is surrogate marker of IL6 (5).
- Interpretation of tests and likely modification of treatment – Clinical picture like day of onset , disease modification agents taken by patient , signs and symptoms to be taken into account before interpreting reports . No single marker should be chased without correlating clinical signs and symptoms.
  1) Significant rise in D Dimer or value >1 µg/mL escalate the dose of heparin . Remember D-dimer can be elevated in pregnancy, malignancy, trauma, liver disease (decreased clearance), heart disease, sepsis or as a result of hemodialysis, CPR or recent surgery.
  2) Significant increase in markers like CRP (more than 100) , IL 6 (>80 pg/mL), Ferritin (more than 700), LDH (more than 300) or rising 3 to 6 times from baseline indicates cytokine storm (along with clinical features) – High dose steroids and anti cytokine drugs like tocilizumab/Itolizumab can be given . Note that after giving anti IL6 there can be transient rise in IL6 (5) .
  3) If ferritin rise is out of proportional (more than 4000) with deranged LFT, remitting high grade fever , appearance of new pulmonary and neurological symptoms and appearance of cytopenia, macrophage activation syndrome/hemophagocytic lymphohistiocytosis (HLH) should be considered after ruling out sepsis. This entity may require high dose steroids and drugs like anakinra (3) .

	Mild	Moderate	Severe
Clinical Criteria			
SpO_2	> 94 % in Room Air	90 - 94 % in Room Air	< 90 % in Room Air
RR	< 24 / min	24 – 30	> 30
SpO_2 after 6 minute walk (this test is contraindicated if base line SpO_2 is less than 95)	No significant	drop of more than 4 (or base line less than 94%)	Test is contraindicated
CT Chest Criteria - (should not be used as routine, clinically correlated)	No Pneumonia Normal or < 25 % Grade I	Pneumonia + 25 % - 75 % Grade II / III	Pneumonia ++ 75 % to 100 % Grade IV

Lung ultrasound (6) (clinical correlation with follow up scans) (interrupted pleural line with different grade of B lines) Ultrasound lung has good correlation with CT scan chest.		Separated (scattered) B-lines, lateral and interscapular area.	Confluent B lines bilateral anterior upper area along with interscapular and lateral area. Consolidation.
Clinical targets and red flag signs (shift the patient to HDU , ICU or increase the support) (4)	Chest pain , breathlessness , heaviness in chest , mental confusion , decreased urine output , poor oral intake , persistent vomiting , bluish discoloration of lips and nails , drop in SpO_2 from baseline (less than 94 or by 4 after 6 min walk), high grade fever (more than 102 degree F) persisting after 5 days of symptom onset.	Target SpO_2 92 to 96% (COPD , chronic lung disease – 88 to 92%) Watch for respiratory distress , work of breathing , accessory muscles of respiration , poor sensorium , increasing requirement of oxygen to maintain targets (more than 5 litres) . Arterial Blood gas if done showing PF ration less than 300 , $PaCO_2$ rising , hemodynamically unstable.	Target SpO_2 > 90 % in non pregnant, $SpO_2 \geq$ 92- 96% in pregnant patients. Recognise septic shock and treat persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L in adults .
Significant laboratory findings Should be interpreted with clinical course and treatment received (as general rule 3 to 6 times rise from baseline is considered to be significant) (5 ,7)	**LAB TEST** NLR (neutrophil lymphocyte ratio) CRP (mg /L) Ferritin (ng/mL) D-Dimer (ng/mL) LDH (U/L) IL6 (pg/mL)	**NORMAL** < 3.5 < 40 < 500 < 0.5 < 300 < 4.8	**SIGNIFICANT** > 5.5 (pre steroids) > 100 and rising > 700 and rising > 1.0 > 400 and rising > 80 and rising (before receiving anti IL6)
TREATMENT	**Mild** Paracetamol 500mg to 650 mg sos T. Vitamin C 500 mg BD Zinc 50 mg BD Vitamin D 60000 one sachet stat	**Moderate** Paracetamol 650 mg TDS T. Vitamin C 500 mg TDS Zinc 50 mg BD Vitamin D 60000 one sachet stat	**Severe** Inj Paracetamol T. Vitamin C 500 mg TDS Zinc 50 mg BD Vitamin D 60000 one sachet stat
Fluids (Avoid overzealous use of furosemide and hypovolemia)	Adequate Hydration - Oral	Adequate Hydration - NS	Conservative Fluids

Drugs (4) HCQ (hydroxychloroquine), Ivermectin , doxycycline, azithromycin benefits till date are not proven. HCQ not indicated in less than 15 year age. **Antibiotics** - If secondary infection is suspected – Procal > 0.2 T. Azithromycin 500 mg OD x 5 Days (or) T. AmoxClav 625 TDS x 5 days or Injection Ceftrioxone 1 gram twice a day if admitted in moderate to severe case.	HCQ Day 1 - 400 mg BD followed by 200 mg BD x 4 Days (avoid in cardiac disease or if QTc > 480 ms) 200 BD if already on HCQ prophylaxis OR Ivermectin 12mg (single dose) with Doxycycline (100 mg bd x 5 days) if not tolerating HCQ. **Drugs to be given in mild disease only if patient belongs to high risk category.**	T. HCQ Day 1- 400 mg BD followed by 200 mg BD x 4 Days OR Ivermectin 12mg (single dose) with Doxycycline (100 mg bd x 5 days) if not tolerating HCQ.	T. HCQ Day 1- 400 mg BD followed by 200 mg BD x 4 Days OR Ivermectin 12mg (single dose) with Doxycycline (100 mg bd x 5 days) if not tolerating HCQ.
Anticoagulation Contraindicated if HAS – BLED Score more than 3 indicates high risk of bleeding – (HAS-BLED SCORE-Hypertension 1point, abnormal renal function 1point, abnormal liver function 1point , stroke 1point , labile INR 1point , alcohol 1point) ☞Also contraindicated in active bleeding, if emergency surgery is planned, platelets < 20,000/mm^3, BP > 200/120 mm/Hg, fibrinogen level less than 0.5 gm/lit *Use D dimer and Sepsis-Induced Coagulopathy (SIC) score (Sofa score , INR , Platelets counts) if more than equal to 4 – portends high thrombotic risk* Monitoring anti-Xa activity in underweight and obese patients, those with chronic renal failure and in those patients with an increasing D-dimer, aiming for an anti-Xa activity of 0.6-1.1 IUml. ☞ LMWH is given even if coagulation tests are abnormal i.e. prolonged PT or aPTT. abnormal PT or aPTT is not a contraindication for LMWH. *Patient on antiplatelet agents follow ASA/ESC and ISTH guidelines*		Inj. Enoxaparin 40 mg SC OD Inj. Dalteparin 2500 IU SC OD In End stage renal disease UFH (unfractionated heparin) – 5000U SC BD	Inj. Enoxaparin 40 mg SC BD or 0.5 mg /kg in two divided doses .Titrate the dose as per value of D dimer.
Steroids No role of steroids in mild cases. It can harm during viremia phase. ☞ *Do not delay in giving first dose once indicated, if delay is expected for admission oral steroids should be given.*		Inj. Dexamethasone 0.1 – 0.2 mg /kg ≈ 6 mg IV OD x 3 to 5 Days or Inj. Methyl Prednisolone 0.5 -1 mg/kg ≈ 40 to 60mg x 3 to 5 Days. ☞ *Avoid Dexamethasone if Remdesevir is planned*	Inj. Dexamethasone 0.2 – 0.4 mg /kg ≈ 6 mg IV BD x 5 to 7 Days or Inj. Methyl Prednisolone 1.0 -2.0 mg/kg ≈ 80 mg x 5 to 7 Days (increase the dose if already given). ☞ *In patients with an increasing CRP or worsening clinical status increase the dose to 80 mg q 12 hourly, then titrate down as appropriate.*

Respiratory support If ICU backup not available and patient deteriorating shift the patient after arranging bed with ventilator, transportation should be done very carefully as it carries risk.	Oxygen by non rebreathing mask. If HFNC or nasal cannula used then apply surgical mask or N 95 mask over it . Try to avoid intubation at this stage . Rescue therapies like awake prone ventilation , anti cytokine drugs like tocilizumab can be tried.	NRM (10 -15 lit / min) ↓ HFNC (10 - 60 lit / min) ↓ BIPAP (PEEP 5-10 cm H20;PIP 20) ↓ Invasive mechanical ventilation (ARDS Protocol)
Prone ventilation 	Awake proning if SpO_2 <94% on FiO_2 40% by either venturi facemask or high flow nasal cannula - 30 to 120 mins prone - 30 to 120 mins left lateral - 30 to 120 mins right lateral - 30 to 120 mins upright – Contraindicated in altered mental status and hemodynamic instability, pregnancy , vomiting, abdominal wound, unstable pelvic/spinal lesions. Before proning increase fiO_2 to 100 percent for five minutes.	Prone Ventilation after intubation (16 to 18 hrs / Day) When to start proning ? P/F ratio < 150, fiO_2 > 0.6 and PEEP > 5 cm H_2O. When to stop proning ? When P/F exceeds 150 on fiO_2 < 0.6 and < 6 PEEP

Therapies recommended in specific conditions and complication

Mild

Favipiravir – Can be given to mild to moderate cases of high risk group within 10 days of symptoms onset. It offers rapid reduction in viral load within 4 days & provides faster symptomatic and radiological improvement.
Dose - 1,800mg (9 tablets) twice daily on day one, followed by 800mg (4 tablets) twice daily up to day 14.
Contraindications - Blood Alanine transaminase/aspartate aminotransferase (ALT/AST) levels > 5 times the upper limit of normal, patients with prolonged QT or PR intervals, second or third degree heart block and arrhythmias, increase of blood uric acid level, diarrhea, decrease of neutrophil count, psychiatric symptoms. Drug is excreted in sperms hence contraception is recommended.

Moderate to severe

Remdesivir - *Indication* - Can be given to high risk group within 12 days of symptoms onset, oxygen saturation of 94% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less (moderate disease)
Dose - 200mg IV OD on Day 1 and 100 mg IV OD x 4 Days (total 5 days)
Note - During infusion watch for hypotension , sweating
Contraindication – Blood Alanine transaminase/aspartate aminotransferase (ALT/AST) levels > 5 times the upper limit of normal on laboratory results, pregnancy, lactation, severe renal impairment (estimated glomerular filtration rate <30 ml per minute per 1.73m square)
Drug interaction – HCQ , Dexamethasone.

In patient with COVID Associated Coagulopathy (CAC) who is actively bleeding.

1. Transfuse platelets if plaletlet count is < 40,000/mm^3
2. Four units of FFP (Fresh Frozen Plasma) if INR is above 1.8.
3. Cryoprecipitate 10 units if fibrinogen is less than 1.5 gm/lit.

Convalescent Plasma Therapy

Indication - Moderate disease before day 10 of symptoms.

Prerequisite – Check IgG level of patient - if not detectable only then plasma should be given.

Assessment of donor for eligibility – 18 to 60 year old with weight > 55 kg without uncontrollable co morbidity, male, nulliparous females, recovered from COVID 19 for minimum 14 days (RT-PCR negative before donation), 28 days (no RT-PCR required), IgG antibodies > 1: 640 or antibodies detectable by chemiluminescent immunoassay or ELISA.

☞ Use should be avoided in patients with IgA deficiency or immunoglobulin allergy.

Dose : 4 to 13 ml/kg (usually 200 ml single dose another 200 ml can be given after 24 hours)

Blood group – Recipient blood group O can receive from O, A, B, AB . AB from AB only . A from A and AB , B from B and AB.

Salvage Treatment (3)

1) **Tocilizumab**- *Indication* - Worsening respiratory distress , high grade fever with chills and rigors , with increasing oxygen (PF ratio <300) , elevated levels of cytokines, including IL-6 (at least 3 times the base level).
Precautions – Absence of infection (systemic bacterial and fungal), procalcitonin <0.5 ng/mL, ALT<500 U/L , Platelet <100000/mm^3 ANC < 2000/mm^3, contraindicated in people living with HIV (PLHIV)

☞ Informed consent to be taken
Dose - 4 to 8 mg/kg (usual dose: 400 mg/dose; maximum: 800 mg/dose) as a single dose; may repeat dose in ≥12 hours in patients who remain febrile within 24 hours of initial dose.

☞ No use of immediately repeating value of IL6 after dose of tocilizumab as there is natural rise due to receptor blockage .

2) **Itolizumab (Alzumab) -** Humanized IgG1 monoclonal antibody. Act by binding to CD6, down regulates T cell activation, causes reduction in synthesis of pro-inflammatory cytokines.
Contraindication – Patients with hepatic and renal impairment.
Infusion and dose – 1.6 mg /kg or 100 mg (4 vials - 25mg/5mL) in 250 ml NS over 6 hours.

☞ Second dose if required can be given after 7 days.

3) **High dose corticosteroids** - 120 -250 mg (3)methylprednisolone q 6-8 hourly in patients with HLH.

4) **Plasma exchange** - Should be considered in patients with progressive oxygenation failure despite corticosteroid therapy as well as in patients with severe HLH. Patients may require up to 5 exchanges. FFP is required for the exchange.

5) **Thrombolysis** - Recombinant tissue plasminogen activator (rtPA) - In patients with a large dead-space ventilation i.e. high PaCO2 despite adequate minute ventilation consider "Half-dose rTPA" to improve pulmonary microvascular blood flow; 25mg of tPA over 2 hours followed by a 25mg tPA infusion administered over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg followed by full anticoagulation(3) .

6) **Adsorption of cytokines by filter (CytoSorb filter)**(3)- CytoSorb use has generally been associated with a marked reduction in cytokine storm and inflammation, improved lung function, weaning from mechanical ventilation, and a reversal of septic shock.
Indications - Not well defined – Refractory oxygenation with low PF ratio less than 150, Early use – Refractory cytokine storm persisting despite high dose steroids , anti IL6 , prone awake ventilation .

☞ Due to the large size of tocilizumab (148 kDa), convalescent plasma antibodies (>150 kDa), and other biologics of similar size, these are not expected to be removed by CytoSorb.
Drawback – It may clear anti-inflammatory cytokines , hydroxycholoroquine and azithromycin.

7) **Anakinra** (competitively inhibits IL-1 binding to the interleukin-1 type I receptor) may be considered in treatment failure of refractory HLH (3).
Dose – 100 mg bolus followed by a 2 mg/kg per day infusion for 24 hours.

8) **ECMO**(3) - Role is doubtful as unlike "typical ARDS" patients do not progress into a resolution phase. Rather, patients with COVID-19 progress to a severe fibro-proliferative phase and ventilator dependency. ECMO in these patients would likely to serve little purpose. May be used in < 60 yrs and no severe comorbidities/organ failure .

Weaning of the therapy

(Abrupt weaning of steroid not recommended due to rebound symptoms)

- Clinically – decrease in RR, breathlessness, oxygen requirement
- If D Dimer, ferritin normal after 3 days – shift to oral prednisolone – taper over next 5 days
- If patient receiving high dose methylprednisolone for HLH reduce the dose once ferritin is reduced by 15% of highest value [3]
- Anticoagulant may be continued for two weeks after discharge.

DISCHARGE CRITERIA	Mild	Moderate	Severe
Update from CDC *(17th July 2020)* - Patients can be discharged from the healthcare facility whenever clinically indicated . A test-based strategy is no longer recommended unless patient is severely immunocompromised. *Following are duration of Transmission-Based precautions/discharge criteria* **1 Mild to moderate** - At least 10 days since symptoms and at least 24 hours have passed since last fever. **2 Severe to critical or immunocompromised-** At least 20 days since first symptoms and at least 24 hours since last fever.	10 Days from symptom onset, RT-PCR not required.	No fever and breathlessness for 72 hours and no drop in SpO_2 less than 90% after minimal walk (off oxygen) 10 Days from symptom onset RT-PCR, not required.	No fever and breathlessness for 72 hours and no drop in SpO_2 less than 90% after minimal walk (off oxygen) After clinical recovery repeat RT-PCR should be done [4]. If swab negative, transfer to non covid care ward – if clinical recovery is delayed.

☞ Above recommendations are based on present knowledge and guidelines published by Govt. of India. They might change as per new knowledge and evidence.

MANAGEMENT IN CHILDREN

Management principles of adolescent and adults are same . In this section we will focus on infants who have highest risk of severe disease and children with Multisystem Inflammatory Syndrome which is observed in patient after 2 to 4 weeks of COVID-19. Data on COVID-19 in children is scarce , despite confirmed numbers in adults are increasing rapidly over the globe.

Symptoms and disease spectrum

1) Gastrointestinal symptoms of vomiting and diarrhea appear to be more common in pediatric patients as compared to adults
2) In severe cases of pediatric COVID 19 there can be two types of presentation . First one is typical cytokine storm as described in adult COVID 19 with predominant HLH like picture . Second a Multisystem Inflammatory Syndrome in Children (MIS-C) has also been described with various presentations ranging from mild inflammation to severe shock with multiorgan involvement . *(figure 3 see on last page)*
3) In many patients there is overlap of features of COVID 19 with cytokine storm, HLH, MIS-C (Multisystem inflammatory syndrome in children suspected) and Kawasaki disease. Inflammatory pathology appears to be more localised within the lung tissue in SARS-CoV-2 infection and systemic inflammatory markers are generally lower than in these HLH and MIS-C related syndromes(8).

Investigations

1) In children less than 2 years with critical disease rule out SCID(Severe Combined Immunodeficiency) - CBC, tlc, dlc, platelets, CD3, CD4, CD8, CD19, natural killer (NK) cell, CD4:CD8 ratio and quantitative immunoglobulins.
   ☞ If total lymphocyte count of ≤3,400 cells/µL at birth, ≤3,900 cells/µL at 5-6 months suspect lymphopenia due to immunodeficiency and not due to COVID 19 (only 3% of children has lymphopenia) (9) .
2) Send CD 25 (marker of familial HLH) along with CRP, ferritin , Ddimer and IL6 in children < 2year old with critical disease (10).
3) Chest Xray should be done in all moderate to severe cases .
4) If Multisystem inflammatory syndrome in children suspected get urinalysis, coagulation studies, troponin I, brain natriuretic peptide (BNP) or NT-pro-BNP, COVID 19 antibodies, blood culture, procalcitonin , echocardiography, ultrasound abdomen done.

	Mild	Moderate	Severe /Critical
	No oxygen requirement – Parents should be trained to recognise red flag signs - difficulty in breathing/fast or shallow breathing (for infants: grunting, inability to breastfeed), blue lips or face, chest pain, new confusion, inability to awaken/not interacting when awake, inability to drink or keep down any liquids .	Dyspnoea , 90 - 94 % in room air. Less than 2 month RR more than 60 , 2 to 11 month more than 50 , 1-5 year more than 40 .	1) Central cyanosis or SpO_2 < 90%; severe respiratory distress , danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. 2)ARDS 3)Septic shock 4)Altered consciousness 5)Multi-organ failure **Acute respiratory distress syndrome**: (10,11)Worsening respiratory symptoms 1 week after disease onset due to SARS-CoV-2 with new opacities on chest imaging not explained by cardiac failure or volume overload and with a partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio ≤300 mmHg, or an SpO_2/ FiO_2 < 264 (SF ratio) during noninvasive ventilation, or an oxygenation index > 4, or an oxygen saturation index (OSI) > 5 during invasive mechanical ventilation .

Mild

1) Paracetamol
2) NSAID use is not contraindicated
3) Zinc - 20 mg / day (>6 months of age) once a day for 14 days.
   10 mg/day (< 6 months of age) once a day for 14 days.
   Vit C - 50 -100 mg/ day once a day for 7 days
   No anti viral therapy needed.

Moderate to severe (9,10)

Remdesivir - May be given compassionate use in very critical patient .
Dose >3.5 to < 40 kg - 5mg/kg loading dose, then 2.5mg/kg once daily x 5 days, > 40 kg 200mg IV OD on Day 1 and 100 mg IV OD x 4 Days (total 5 days)

- ☞ During infusion watch for hypotension and sweating.
- ☞ Watch for liver dysfunction.

Anticoagulation – Presently there are no recommendation like adolescents and adults (9)
Indication 1- Those with indwelling central or peripheral central venous catheters. (*Dose* - Subcutaneous enoxaparin < 2 months: 0.75 mg/kg/dose q12 h; ≥2 months: 0.5 mg/kg/dose q12 h - Anti-Xa factor target: 0.3–0.5 IU/ml)
Indication 2- For high risk, critically ill patient with hyperinflammatory state *(Dose*- < 2 months : 1.5 mg/kg/dose q12 h; ≥2 months 1mg/kg/dose q12 h - Anti-Xa factor target: 0.5–1 IU/ml).

Rescue therapies – like steroids, tocilizumab, anakinra should be considered on a case by case basis . Bacterial, fungal and tuberculosis infections should be ruled out before giving these therapies.

Steroids (10)

Indication -

a) Respiratory support (oxygen or invasive mechanical ventilation)

b) An underlying condition requiring chronic steroid treatment.

Dose- Dexamethasone - 0.15mg/kg once daily (Max: 6 mg) OD 10 days

Prednisolone - 1 mg/kg once daily (Max: 40 mg) x 10 days

Methylprednisolone - 0.8 mg/kg once daily (Max: 32 mg) x 10 days

Pulse Methylprednisolone should be used in high-risk KD features, MIS-C *(see on last page figure 3)*

- 10 mg/kg-30 mg/kg/day for 1-3 days followed by 2mg /kg/day.

Convalescent Plasma - can be given on compassionate basis.

Salvage Treatments (9,10)

1) Tocilizumab

Indication –

a) Worsening respiratory distress , with failure of steroids and cytokine storm.

b) MIS-C - in severe presentation if fevers > 24 hrs post steroids / IVIG.

Dose- < 30 kg: 12 mg/kg. (max 800 mg)

≥ 30 kg: 8 mg/kg. (max 800 mg) as a single dose; may repeat dose in ≥12 hours in patients who remain febrile within 24 hours of initial dose.

2) Anakinra

Indication -

Consider in severe MIS -C if fever persisting > 24 hrs post steroids and IVIG. It should be considered as drug of choice in refractory hyper inflammatory syndrome.

Dose- < 20 kg - 2mg/kg stat loading dose, followed by a continuous infusion of 2mg/kg/day. Increase dose by 2mg/kg/day every 12 hours if unresponsive.

☞ Maximum dose 12mg/kg/day (400mg excluding loading dose)

Caution - anaphylaxis, neutropenia, eosinophilia, transaminitis, immunosuppression.

3) Intravenous immunoglobin –

Indication - KD features and/or coronary artery changes, MIS-C

Dose- 2 g/kg, (max dose 100g) over 24 hours.

☞ 1gm/kg if cardiac disfunction is suspected as these patients do not tolerate large amount of fluid.

4) Plasma exchange -

Indication -

In critically ill children with COVID-19, thrombocytopenia-associated multiple organ failure. (TAMOF : platelet counts less than 1 lakh and two or more failing organs)

5) ECMO - ECMO should be considered in COVID-19 -infected pediatric patients to manage ARDS and/or cardiac failure (myocarditis, arrhythmias, pulmonary embolism) if conventional treatment fails .

Multisystem inflammatory syndrome in children

(***MIS-C***) (8,10 ,11) *(refer to figure 3)*

Definition of MIS C - A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease.Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis.

☞Antibody test for SARS-CoV-2 may be positive (90 percent), RT PCR may be positive in 10 percent cases.

Empirical antibiotics -

In patient with TSS (toxic shock syndrome) like MIS-C

1) Milder illness ceftriaxone.

2) If GI symptoms are predominant add metronidazole.

3) In cases of severe illness or shock - vancomycin, clindamycin, and ceftriaxone.

☞ Once cultures are negative antibiotics to be discontinued

Use of aspirin –

1) Treatment with aspirin should be avoided in patients with a platelet count ≤80,000mm^3

2) MIS-C patients with CAAs (coronary abnormality) and a maximal z-score of 2.5-10.0 should be treated with low dose aspirin. Patients with a z-score ≥10.0 should be treated with low dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xa level 0.5-1.0) or warfarin

Discharge criteria and follow-up

Clinical criteria - Eating and drinking adequately, heart failure symptoms controlled with oral medications (if applicable). 48 h without supplemental oxygen, 48 h without fever, 48 h off vasopressors.

Echocardiography - stable or improved : ventricular function, coronary artery abnormalities; and valve function.

Laboratory parameters - Three to four days of down trending inflammatory markers (ferritin, CRP, DDimer), troponin consistently declining and < 1.0 ng/mL.

Repeat Echo frequency -

1) Initial normal: 1-2 weeks and 4-6 weeks

2) Initial abnormal with CA z-score >2.5: repeat Q 2-3 days until CA aneurysm stable, then weekly until discharge.

Steroid use and tapering –

1) For mild cases consider methylprednisolone 2 mg/kg/day (max of 40-60 mg per day) then taper over 2-3 weeks.

2) For moderate cases consider MPS 10 mg/kg x 1 followed by 2mg/ kg/day with 2-3 week taper.

3) For severe cases (e.g. ICU) consider methylprednisolone 20-30mg/kg/day for 1-3 days, then 2mg/kg/day and taper over 6-8 weeks .

Aspirin – High dose till afebrile for 48 hours then shift to low dose (see figure 3) .On followup continue for 4 to 6 weeks after normal echocardiography .

LMWH – Continue for 2 weeks after normal echocardiography.

Indications for longer outpatient therapeutic enoxaparin dosing include : CAA with z-score >10.0 (indefinite treatment), documented thrombosis (treatment for ≥3 months pending thrombus resolution), or ongoing moderate to severe LV dysfunction

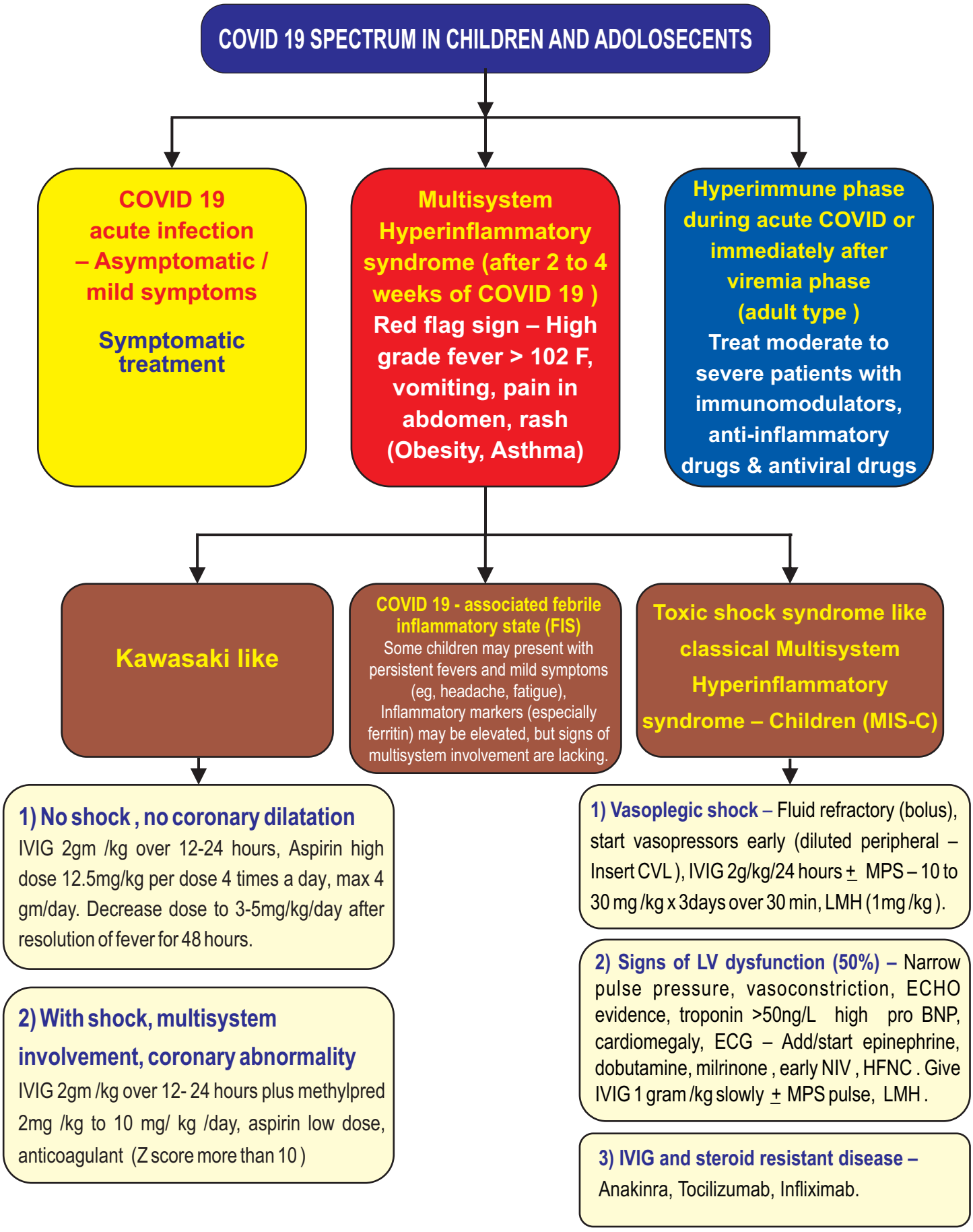


Fig. 3 *Management of COVID 19 and MISC in Children*

Pharmacologic therapies in COVID 19 in children and adults		
Agent	Drug	Optimal clinical timing
Antiviral	Remdesivir , favipiravir	Before day 10-12 of symptoms
Immune enhancement	Convalescent plasma in hospital	Before day 10 of symptoms
Anti-inflammatory	Corticosteroids Interleukin 1 receptor antagonist Interleukin 6 inhibitor	Day 5 to 20

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