

**COVID-19 Outbreak Control and Prevention State Cell  
Health & Family Welfare Department  
Government of Kerala**

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**Addendum – Constitution of State Medical Board – Reg  
NO: 38/ 31/F2/2020/Health- 5<sup>th</sup> Aug 2021**

In superseding all the previous advisories, guidelines regarding the patient management and treatment, the revised updated Treatment Guidelines Version 4 is issued for practicing in the State of Kerala.

The Guidelines are attached as an Annexure. The Guidelines shall be followed up by the treating teams and the Hospital Medical Board. If there are any doubts, the treating teams may consult the State Medical Board.

A handwritten signature in green ink, appearing to read 'Rajm'.

**PRINCIPAL SECRETARY**

Health and Family Welfare Department , Govt of Kerala

# **COVID-19: Treatment Guidelines for Kerala state**

**Version 4**



**Aug 2021**

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## **1. Introduction**

The COVID – 19 pandemic has been evolving since it first surfaced in China. With more data and inputs from around the world, there is now better understanding about the disease epidemiology, transmission dynamics and treatment. Data from the ACTT, RECOVERY, ACTT-2, SOLIDARITY, STOP-COVID and others have brought to light the role of antivirals and other therapeutic strategies like immunomodulators in the management of COVID-19. The results and valuable insights from latest research have been synthesized into this document, which will be updated in a timely fashion to reflect further breakthroughs and development in the treatment of SARS-CoV-2 infection.

The guidelines have been revised with the aim of bringing down case fatality in Kerala further down by planned interventions in very high-risk groups. A chapter on management of COVID 19 in pregnancy has been added keeping in mind the increasing number of COVID related maternal deaths and near miss observed during the second wave compared to first wave in Kerala.

This document has been developed as a clinical guideline to streamline the treatment of SARS- CoV2 infection based on the available evidence from across the world and also based on data and experience from Kerala. The best practices from other countries and institutions have been captured into this document. It is a “living” document and will be updated from time to time based on evolving evidence.

## 2. Case Definitions

### Suspect case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;

OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset;

OR

C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

### Probable case

A. A suspect case for whom testing for the COVID-19 virus is inconclusive.

OR

B. A suspect case for whom testing could not be performed for any reason.

### Confirmed case

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

#### NICE SURVEILLANCE DEFINITIONS OF COVID 19 INFECTION

ACUTE COVID 19- signs and symptoms of COVID 19 persisting for upto 4 weeks

Ongoing symptomatic COVID 19: Signs and symptoms of COVID 19 from 4 to 12 weeks

POST COVID SYNDROME: Signs and symptoms that develop during or after an infection consistent with COVID 19, continue for more than 12 weeks and are not explained by an alternative diagnosis

Long COVID includes both ongoing symptomatic COVID and post COVID syndrome

SARS CoV 2 infection should also be suspected in patients who present with stroke in young, multi vessel / large vessel stroke, Kawasaki like illness, Multi system inflammatory syndrome, hyperinflammatory shock, toxic shock syndrome like illness in children, acute myocardial infarction, Guillain-Barre syndrome, viral encephalitis, ADEM, olfactory/gustatory dysfunction or conjunctivitis.

### 3. Clinical Categorization

#### Categories based on symptomatology

<b>A</b>	Mild sore throat / cough / rhinitis /diarrhea/anosmia
<b>B</b>	<p>Fever and/or severe sore throat / cough /diarrhea/anosmia</p> <p style="text-align: center;">OR</p> <p>Category-A with any one of</p> <ul style="list-style-type: none"> <li>• Lung/ heart / liver/ kidney / neurological disease/ Hypertension / haematological disorders/ uncontrolled diabetes/ cancer /HIV-AIDS/ Cardiovascular disease</li> <li>• On long term steroids /immunosuppressive drugs.</li> <li>• Pregnant woman</li> <li>• Age –more than 60 years</li> </ul>
<b>C</b>	<ul style="list-style-type: none"> <li>• Breathlessness, chest pain, drowsiness, fall in blood pressure, haemoptysis, cyanosis [red flag signs]</li> <li>• Children with ILI (influenza like illness) with <i>red flag signs</i> (Somnolence, high/persistent fever, inability to feed well, convulsions, dyspnoea /respiratory distress, etc)</li> <li>• Worsening of underlying chronic conditions</li> </ul>

**\*Categorization should be reassessed every 24-48 hours for Category A & B**

### Clinical Severity Stages

Clinical Severity	Clinical Parameters	Corresponding Category according to state guidelines
Mild	No breathlessness or Hypoxia	A, B
Moderate	<p><b>Adult:</b> dyspnea and/ or hypoxia, fever, cough, SpO<sub>2</sub> ≤ 94% (range 90-94%) on room air, Respiratory Rate ≥ 24 per minute.</p> <p><b>Child</b> – dyspnea and or hypoxia, fever, cough, including SpO<sub>2</sub> ≤ 94% (range 90-94%) on room air, Respiratory Rate ≥ 24 per minute. Fast breathing (in breaths/min): &lt; 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40</p>	C
Severe	<p><b>Adult:</b> Pneumonia plus one of</p> <ul style="list-style-type: none"> <li>▸ respiratory rate ≥ 30 breaths/min</li> <li>▸ severe respiratory distress</li> <li>▸ SpO<sub>2</sub> ≤ 90% on room air.</li> </ul> <p><b>Child:</b> cough/dyspnoea, plus one of</p> <ul style="list-style-type: none"> <li>▸ central cyanosis or SpO<sub>2</sub> ≤ 90%;</li> <li>▸ severe respiratory distress (e.g. grunting, chest in-drawing);</li> <li>▸ signs of pneumonia with danger signs: (inability to breastfeed or drink, lethargy, unconsciousness, or convulsions).</li> <li>▸ Other signs of pneumonia like chest in drawing, fast breathing (in breaths/min): &lt; 2 months ≥ 60; 2–11 months ≥ 50; 1–5 years ≥ 40.</li> </ul>	C

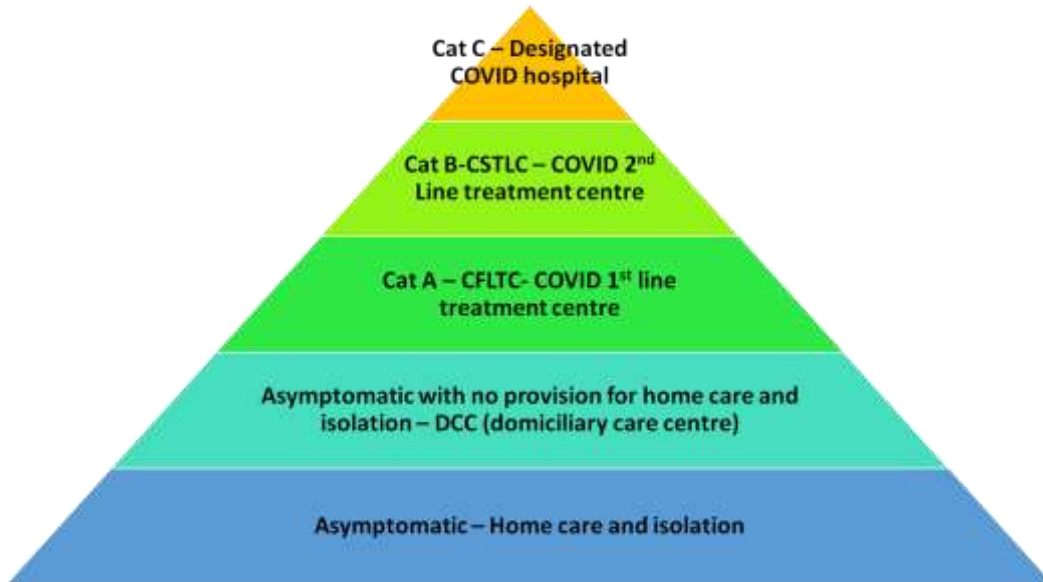
### Severity categories for treatment purpose

Mild	Respiratory Rate < 24/min, SpO <sub>2</sub> > 94 on room air
Moderate	Respiratory rate between 24-29, SpO <sub>2</sub> between 91-94 on room air
Severe	Respiratory Rate ≥ 30, SpO <sub>2</sub> < 90

## 4. Treatment algorithm

In the current stage of the pandemic, Kerala follows the five-tier system of COVID care

THE FIVE TIER COVID 19 CARE PYRAMID - KERALA





### Laboratory investigation for proven COVID 19 patients

At Admission	CBC, RFT, LFT, CRP, RBS, S. Electrolytes, ECG, Pulse oximetry.
If clinically Indicated	Portable CXR, HIV, HBsAg, HCV, D-Dimer, Ferritin, LDH, CPK, procalcitonin, Blood culture, TROP T/I, HRCT Thorax [only in case of worsening]
To repeat Every 48 hours if clinically deteriorating.	CBC, Creatinine, AST/ALT, CRP, LDH, CPK, Ferritin, D Dimer.
For Immunocompromised patients eg: Transplant recipients, HIV	Tests to rule out opportunistic infections like Mycobacterium tuberculosis, pneumocystis jiroveci etc

### Identification of high-risk patients

Co-morbidities	Clinical assessment	Laboratory values
Uncontrolled diabetes [HbA1C $\geq$ 8%]	Hypoxia – SpO <sub>2</sub> $\leq$ 94 % on room air	CRP > 100 mg /L
Hypertension	Tachycardia PR > 110/min	CPK > twice upper limit of normal
Cardiovascular disease	Respiratory distress RR > 24/min	Ferritin > 300mcg/L
Preexisting pulmonary disease	Hypotension BP < 90 systolic, 60mm Hg Diastolic	LDH > 245 U /L
CKD	Altered sensorium	TROP T elevation
CLD	PAO <sub>2</sub> /FiO <sub>2</sub> < 300 mm of Hg	D Dimer > 1000ng/ml
On immunosuppressives / biological		
HIV CD4 <200 / congenital immunodeficiency disorders		Multi organ dysfunction
Age > 65 yrs.		*ALC < 0.8
BMI > 30 Kg/m <sup>2</sup>		#NLR >3.13

\*ALC – Absolute lymphocyte count #NLR – Neutrophil lymphocyte ratio [NLR –should be calculated prior to steroid administration]

## CT-guided approach to diagnosis in a suspected COVID-19 patient

In symptomatic patients with suspected COVID – 19, HRCT thorax may be considered for diagnosis of COVID –19 when initial RT-PCR testing is negative. CT guided approach should be used in RTPCR negative cases with high clinical index of suspicion of COVID – 19.

Imaging classification	Rationale	CT appearance
<b>Typical appearance</b>	Commonly reported imaging features of greater specificity for COVID 19 pneumonia	Peripheral bilateral GGO with or without consolidation or visible intra lobular lines (‘crazy paving’) Multifocal GGO of rounded morphology with or without consolidation or visible intra lobular lines (‘crazy paving’) Reverse halo sign or other signs of organizing pneumonia
<b>Indeterminate appearance</b>	Nonspecific imaging features of COVID 19 pneumonia	<b>Absence of typical features AND Presence of</b> Multifocal diffuse perihilar or unilateral GGO with or without consolidation lacking a specific distribution and are non-rounded or non-peripheral Few very small GGO with a non-rounded and non-peripheral distribution
<b>Atypical Features</b>	Uncommonly or not reported features of COVID-19 pneumonia	<b>Absence of typical features or indeterminate features AND Presence of</b> Isolated lobar or segmental consolidation without GGO Discrete small nodules (centrilobar, tree in bud) Lung cavitation Smooth interlobular septal thickening with pleural effusion
<b>Negative for pneumonia</b>	No features of pneumonia	No CT features to suggest pneumonia

GGO – Ground Glass Opacities

Reference: Simpson S, Kay FY, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, Litt D. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society

of Thoracic Radiology, the American College of Radiology, and RSNA. Radiology: Cardiothoracic Imaging, in press. <https://doi.org/10.1148/ryct.2020200152>

<b>Typical Features for Pulmonary Involvement of COVID-19</b>
<b>Obligatory Features</b>
Ground-glass opacities, with or without consolidations, in lung regions close to visceral pleural surfaces, including the fissures (subpleural sparing is allowed) and multifocal bilateral distribution
<b>Confirmatory Patterns</b>
Ground-glass regions
Unsharp demarcation, (half) rounded shape
Sharp demarcation, outlining the shape of multiple adjacent secondary pulmonary lobules
Crazy paving
Patterns compatible with organizing pneumonia
Thickened vessels within parenchymal abnormalities found in all confirmatory patterns

<b>Overview of CO-RADS Categories and the Corresponding Level of Suspicion for Pulmonary Involvement in COVID-19</b>		
<b>CO-RADS Category</b>	<b>Level of Suspicion for Pulmonary Involvement of COVID-19</b>	<b>Summary</b>
0	Not interpretable	Scan technically insufficient for assigning a score
1	Very low	Normal or noninfectious
2	Low	Typical for other infection but not COVID-19
3	Equivocal/unsure	Features compatible with COVID-19 but also other diseases
4	High	Suspicious for COVID-19
5	Very high	Typical for COVID-19
6	Proven	RT-PCR positive for SARS-CoV-2
Note: CO-RADS = COVID-19 Reporting and Data System, COVID-19 = coronavirus disease 2019, RT-PCR = reverse transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.		

Reference: Prakap M, Everdingen WV, Vellinga TR et al, for the COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19—Definition and Evaluation. Radiology 2020; 296: E97–E104 • <https://doi.org/10.1148/radiol.2020201473>

## **CT SEVERITY INDEX (CTSI)**

### **CTSI**

The severity of the lung involvement on the CT correlates with the severity of the disease.

CTSI is assessed by scoring the percentages of each of the five lobes that is involved:

0. No involvement
1. < 5% involvement
2. 5%-25% involvement
3. 26%-49% involvement
4. 50%-75% involvement
5. > 75% involvement.

The total CT score is the sum of the individual lobar scores and can range from 0 (no involvement) to 25 (maximum involvement), when all the five lobes show more than 75% involvement.

### **CT SEVERITY SCORE**

<b>CT Score</b>	<b>Severity</b>
<8	Mild
8-15	Moderate
>15	Severe

### **Treatment**

- Patients categorized to A, B, C must be further risk stratified into mild, moderate and severe.
- AVOID using NSAIDs other than paracetamol unless absolutely necessary.
- AVOID using nebulized drugs to avoid aerosolization of virus, use MDI instead.
- Oseltamivir should be initiated in all symptomatic patients with influenza like illness till RTPCR/Antigen test result is obtained.
- In patients with COVID-19 pneumonia, secondary bacterial or viral infection is uncommon. Initiation/continuation of antibiotics solely due to COVID-19 is not indicated. Extended duration of fever is typical in COVID-19 patients. Based on literature to date, no unique association between specific pathogens, such as MRSA or *Pseudomonas*, has been made with COVID-19. Antibiotic selection in case of secondary bacterial pneumonia should be as per institutional antibiogram.

- GINA and GOLD guidelines have recommended continuation of inhaled steroids even in patients with COVID-19.
- Currently there are no data to support either starting or stopping ACEI /ARBs in any patients with COVID-19. ACEI /ARB may be continued in patients who are already on them. However, if acute kidney injury, hypotension or other contraindication develops, consider stopping them at that time.
- If secondary pneumonia is not improving on broad-spectrum antibiotics, consider the possibility of CAPA [Covid Associated Pulmonary Aspergillosis] or CAM [Covid associated pulmonary Mucormycosis].

#### **Why routine HRCT imaging of chest in COVID 19 patient is NOT recommended?**

- Nearly two-thirds of persons with asymptomatic COVID 19 have abnormalities on HRCT chest imaging which are non-specific. Most of them do not progress clinically.
- HRCT chest imaging done in first week of illness might underestimate extent of lung involvement.
- Correlation between extent of lung involvement by HRCT imaging of chest and hypoxia is imperfect.
- Repeated radiation exposure from HRCT imaging can pose radiation hazard. So HRCT imaging should be considered only if indicated.

#### **Appropriate clinical indications for HRCT imaging of Chest in COVID 19 patients:**

1. Suspected/confirmed cases of moderate / severe COVID 19 who progressively deteriorate despite optimal therapy to look for pulmonary embolism, invasive fungal infection etc.
2. To diagnose PCR negative SARS COV 2 broncho pneumonia
3. As part of pulmonary rehabilitation to assess the extent of lung damage

## Treatment strategies according to clinical categorization and Risk stratification

Category	Treatment	Precautions
A	Symptomatic treatment	<b><i>Categorization should be reassessed every 24-48 hours for Category A.</i></b> (Chart of respiratory rate, SpO <sub>2</sub> , Single breath count to be maintained)
B	Inhalational budesonide 800 mcg twice a day for 5 to 7 days if fever and cough are persistent beyond five days of disease onset  *Monoclonal antibodies-Casirivimab and imdevimab if indicated for highest risk category	Given via MDI/DPI [metered dose inhaler/dry powder inhaler]  <b><i>Categorization should be reassessed every 24 hours for Category B.</i></b> (Chart of respiratory rate, SpO <sub>2</sub> , Single breath count to be maintained)
C	Inhalational budesonide 800 mcg twice a day for 5 to 7 days if fever and cough are persistent beyond five days of disease onset	<b><i>Severity should be reassessed every 12 hours for Category C.</i></b> (Chart of respiratory rate, SpO <sub>2</sub> , Single breath count to be maintained)
C – moderate severity  (Resp rate between 24-29, SpO <sub>2</sub> between 91-94 on room air)	If duration of symptoms is less than 10 days, Inj Remdesivir 200 mg IV on day 1 followed by 100 mg IV daily for total 5 days  PLUS  Inj Methyl prednisolone 0.5-1 mg/kg/day for 5-10 days  Or  Inj Dexamethasone – 0.1-0.2	Remdesivir [EUA] based on limited available evidence and only in specific circumstances.  If there is no clinical response to the dose of steroid used, as per pulmonologist/Physician directive dose of steroids can be escalated or JAK inhibitors may be added if glycaemic control cannot be optimized on steroids. Duration of steroids should be individualized based on clinical

	<p>mg/kg/day for 5-10 days</p> <p>PLUS</p> <p>Anti-coagulation as per state protocol</p> <p>*JAK inhibitors if indicated.</p>	response.
<p>C – severe signs and symptoms</p> <p>Resp Rate <math>\geq</math> 30, SpO<sub>2</sub> &lt; 90 on room air</p>	<p>If duration of symptoms is less than 10 days, Inj Remdesivir 200 mg IV on day 1 followed by 100 mg IV daily for total 5 days</p> <p>PLUS</p> <p>Inj Methyl prednisolone 1-2 mg/kg/day for 5-10 days</p> <p>Or</p> <p>Inj Dexamethasone – 0.2-0.4 mg/kg/day for 5-10 days</p> <p>PLUS</p> <p>Anticoagulation as per state protocol</p> <p>*Inj Tocilizumab if indicated.</p> <p>*JAK inhibitors if indicated.</p>	<p>Remdesivir is contraindicated in</p> <ul style="list-style-type: none"> <li>• AST/ALT &gt; 5 times Upper limit of normal (ULN) [AST/ALT has to be monitored daily]</li> <li>• Severe renal impairment (i.e., eGFR &lt; 30ml/min/m<sup>2</sup> or need for hemodialysis) [NOT an absolute contraindication]</li> <li>• Pregnancy or lactating females [if benefit outweighs risk may be administered on compassionate ground with informed consent]</li> </ul>
<p><b>REMDESIVIR</b></p> <ul style="list-style-type: none"> <li>• Only in category C – moderate and severe disease</li> <li>• No renal or hepatic dysfunction (eGFR &lt; 30 ml/min/m<sup>2</sup>, AST/ALT &gt; 5 times ULN) – NOT an absolute contraindication</li> </ul>		
<p><b>TOCILIZUMAB</b></p> <p>Tocilizumab in combination with steroids is now recommended in patients with</p> <p>1. Recently hospitalized patients who have been admitted to ICU within the prior 24 hours and who require invasive mechanical ventilation, NIV or HFNC [ &gt;0.4 FiO<sub>2</sub>/30L/min of oxygen flow]</p> <p>OR</p> <p>2. Recently hospitalized patients with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation [CRP &gt;75 mg/L was cut off in RECOVERY trial]</p>		

### **Indications for JAK inhibitors in COVID 19 (Baricitinib / Tofacitinib)**

Diagnosed COVID 19 infection

1. Consider only for patients who have not received Tocilizumab or on mechanical ventilation, who require 8 L O<sub>2</sub> or FiO<sub>2</sub> > 0.4 or higher levels of respiratory support for at least 8 hours and are not improving despite 24 hours of standard care including dexamethasone.
2. In rare circumstance when corticosteroids cannot be used, **baricitinib or tofacitinib may be used** for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation.

Baricitinib or tofacitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

### **Monoclonal Antibodies [Casirivimab and Imdevimab]**

Aim of administration of anti-SARS-COV-2 monoclonal antibodies is to prevent disease progression in highest risk groups. \* So, it has to be administered early in the disease course before hypoxia develops.

It should **NOT BE** administered in

1. Those who require oxygen therapy due to COVID-19; or
2. Those who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and, because of COVID-19, require an increase in oxygen flow rate from baseline.
3. More than 10 days from symptom onset.

\*refer section number 9 Monoclonal antibodies



**Kerala State COVID 19 guidelines Version 3, April 24, 2021**

Treatment guidelines for COVID 19 patients	
<p align="center"><b>Category A</b></p> <p>Symptomatic treatment                      Reassessment every 24-48 hours for change in category                      Monitor for dyspnoea, hypoxia (SpO<sub>2</sub>&lt;94%), high grade fever, severe cough, altered sensorium and excessive fatiguability</p> <p><b><i>Categorization should be reassessed every 24-48 hours for Category A.</i></b>                      (Chart of respiratory rate, SpO<sub>2</sub>, Single breath count t be maintained)</p>	
<p align="center"><b>Category B</b></p> <p>MDI/DPI Budesonide 800mcg twice a day if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset</p> <p><b><i>Categorization should be reassessed every 24 hours for Category B.</i></b>                      (Chart of respiratory rate, SpO<sub>2</sub>, Single breath count t be maintained)</p>	
<p align="center"><b>Category C</b></p> <p>MDI/DPI Budesonide 800mcg twice a day if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset</p> <p><b><i>Severity should be reassessed every 12 hours for Category C.</i></b>                      (Chart of respiratory rate, SpO<sub>2</sub>, Single breath count t be maintained)</p>	
<p><b>Moderate severity (respiratory rate 24-29/min, SpO<sub>2</sub> 91-94 on room air)</b>                      Inj Methyl prednisolone 0.5-1 mg/kg/day for 5-10 days</p> <p align="center">Or</p> <p>Inj Dexamethasone – 0.1-0.2 mg/kg/day for 5-10 days</p> <p align="center">PLUS</p> <p>Anti-coagulation as per state protocol                      *see EUA below</p>	<p><b>Severe (respiratory rate ≥30/min, SpO<sub>2</sub> &lt; 90 on room air)</b>                      Inj Methyl prednisolone 1-2 mg/kg/day for 5-10 days</p> <p align="center">Or</p> <p>Inj Dexamethasone – 0.2-0.4 mg/kg/day for 5-10 days</p> <p align="center">PLUS</p> <p>Anticoagulation as per state protocol                      *See EUA below</p>
<p><u>*EUA/Off label use based on limited available evidence and ONLY in special circumstances</u></p> <p><b>REMEDESIVIR</b></p> <ul style="list-style-type: none"> <li>• Only in category C – moderate and severe disease (ie requiring supplemental oxygen) AND</li> <li>• Within 10 days of symptom onset</li> <li>• No renal or hepatic dysfunction (eGFR &lt; 30ml/min/m<sup>2</sup>, AST/ALT &gt; 5 times ULN) – NOT an absolute contraindication</li> <li>• Recommended dose is 200 mg IV on day 1 followed by 100 mg IV daily for next 4 days</li> </ul>	

## TOCILIZUMAB

When all below categories are met

- Severe disease (preferably within 24 – 48 hours of onset of severe disease / ICU admission)
- Significantly Raised inflammatory markers CRP &/or IL-6 (RECOVERY TRIAL cut off > 75mg/L)
- Not improving despite use of steroids
- No active bacterial / fungal / tubercular infection
- Recommended dose is 8mg/kg (usually a dose of 400 mg in a 60Kg adult; maximum dose 800 mg) in 100ml NS over 1 hour (Single Dose)

## JAK inhibitors in COVID 19 (Baricitinib / Tofacitinib)

Diagnosed COVID 19 infection

1. Consider only for patients who have not received Tocilizumab or on mechanical ventilation, who require 8 L O<sub>2</sub> or FiO<sub>2</sub> > 0.4 or higher levels of respiratory support for at least 8 hours and are not improving despite 24 hours of standard care including dexamethasone/methylprednisolone.
2. In rare circumstance when corticosteroids cannot be used, **baricitinib or tofacitinib may be used** for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation.

\*there should not be any evidence of active tuberculosis / fungal / bacterial infection

BARICITINIB dose 4mg OD for 7-14 days

TOFACITINIB dose 10mg OD for 7 -14 days.

Baricitinib or tofacitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

## Monoclonal Antibodies [Casirivimab and imdevimab]

Aim of administration of anti-SARS-COV-2 monoclonal antibodies is to prevent disease progression in highest risk groups.\* So it has to be administered early in the disease course before hypoxia develops.

It should **NOT BE** administered in

1. Those who require oxygen therapy due to COVID-19; or
2. Those who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and, because of COVID-19, require an increase in oxygen flow rate from baseline.
3. More than 10 days from symptom onset.

\*refer section number 9 Monoclonal antibodies for highest risk groups

**Zinc, Vitamin C and Azithromycin have NO evidence-based role in the treatment or prevention of COVID 19 infection**

**Focus on infection prevention and control and antibiotic stewardship to optimize clinical outcomes in critically ill**

Category A	Category B	Category C
Mild sore throat / cough / rhinitis /diarrhea	Fever and/or severe sore throat / cough  OR Category-A with any one of the following #risk factors <ul style="list-style-type: none"> <li>• Lung/ heart / liver/ kidney / neurological disease/ Hypertension/haematological disorders/ uncontrolled diabetes/ cancer /HIV- AIDS</li> <li>• On long term steroids</li> <li>• Pregnant lady</li> <li>• Age –more than 60 years.</li> </ul>	Breathlessness, chest pain, drowsiness, fall in blood pressure, haemoptysis, cyanosis [red flag signs] Children with ILI (influenza like illness) with <b>red flag signs</b> (Somnolence, high/persistent fever, inability to feed well, convulsions, dyspnoea /respiratory distress, etc). Worsening of underlying chronic conditions

## COVID 19 treatment considerations in pregnancy

1.	For moderate and severe SARS CoV 2 bronchopneumonia, Inj Remdesivir may be considered on a compassionate basis after obtaining informed consent
2.	For moderate and severe SARS Co V 2 bronchopneumonia, corticosteroids are indicated for 10 days or up to discharge whichever is sooner
3.	The selection of steroids depends on the stage of gestation
4.	If steroids are not indicated for fetal lung maturity, Inj Methylprednisolone 40mg IV OD (ie 0.5-1mg/kg) IV OD, oral prednisolone 40 mg once a day or IV hydrocortisone 80mg twice a day for 10 days or until discharge whichever is earlier
5	If steroids are indicated for fetal lung maturity, Intra muscular dexamethasone 6mg every 12 hours for 4 doses then followed by Inj Methylprednisolone 40mg IV OD (ie 0.5-1mg/kg) IV OD, oral prednisolone 40 mg once a day or IV hydrocortisone 80mg twice a day for 10 days or until discharge whichever is earlier
6.	All pregnant women admitted with COVID 19 should be offered prophylactic low molecular heparin unless birth is expected within 12 hours or there is significant risk of haemorrhage. Thromboprophylaxis should be offered for 10 days following discharge.
7.	If women are admitted with confirmed COVID 19 infection within 6 weeks post-partum, thromboprophylaxis should be offered for the duration of hospitalization and continued atleast 10 days after discharge. For those with significant comorbidity, duration of thromboprophylaxis may be extended to 6 weeks post-partum.

*Reference - Corona virus (COVID 19) infection in pregnancy RCOG February 19 2021*

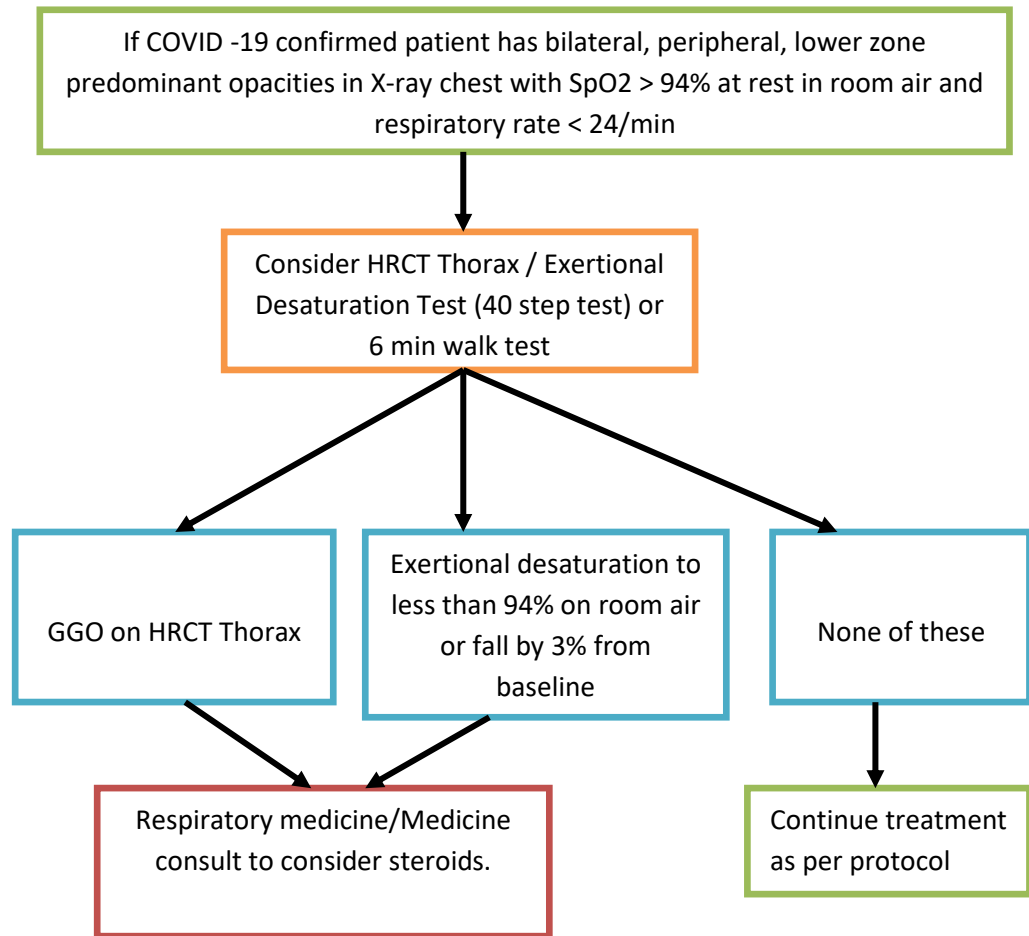
### D Dimer cut offs in normal pregnancy

First Trimester	169-1202 mcg/L
Second trimester	393-3258 mcg/L
Third trimester	551-3333 mcg/L

## Criteria for using Tocilizumab

Criteria for using Tocilizumab	Tocilizumab Regimen
<p>Change in recommendation after publication of REMAP-CAP and RECOVERY trial results</p> <p><b>Tocilizumab in combination with steroids is now recommended in patients with:</b></p> <p>1. Recently hospitalized patients who have been admitted to ICU within the prior 24 hours and who require invasive mechanical ventilation, NIV or HFNC [<math>&gt;0.4</math> FiO<sub>2</sub>/30L/min of oxygen flow]</p> <p>OR</p> <p>2. Recently hospitalized patients with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation [CRP <math>&gt;75</math> mg/L]</p>	<p>8 mg/kg IV (Maximum dose 800 mg) may be repeated once after 12 hours if no clinical improvement.</p> <p><b><u>Toxicities/Monitoring Parameters</u></b></p> <ul style="list-style-type: none"> <li>- Infusion related/ injection site reaction</li> <li>- Monitor LFTs (life threatening hepatotoxicity can occur)</li> <li>- Monitor neutrophils/platelets</li> </ul> <p><b><u>Cautions</u></b></p> <ul style="list-style-type: none"> <li>- Patients with increased risk of GI perforations - Use in pregnant patients must be made on a case-by case-basis with additional discussion and approval from the OB/GYN attending.</li> <li>- ALT/AST 3xULN</li> <li>- Neutropenia (ANC <math>&lt; 0.5</math> K/CUMM)</li> <li>- Thrombocytopenia (<math>&lt; 50</math> K/CUMM)</li> <li>- Latent or active pulmonary tuberculosis</li> <li>- Active bacterial or fungal infection</li> </ul>

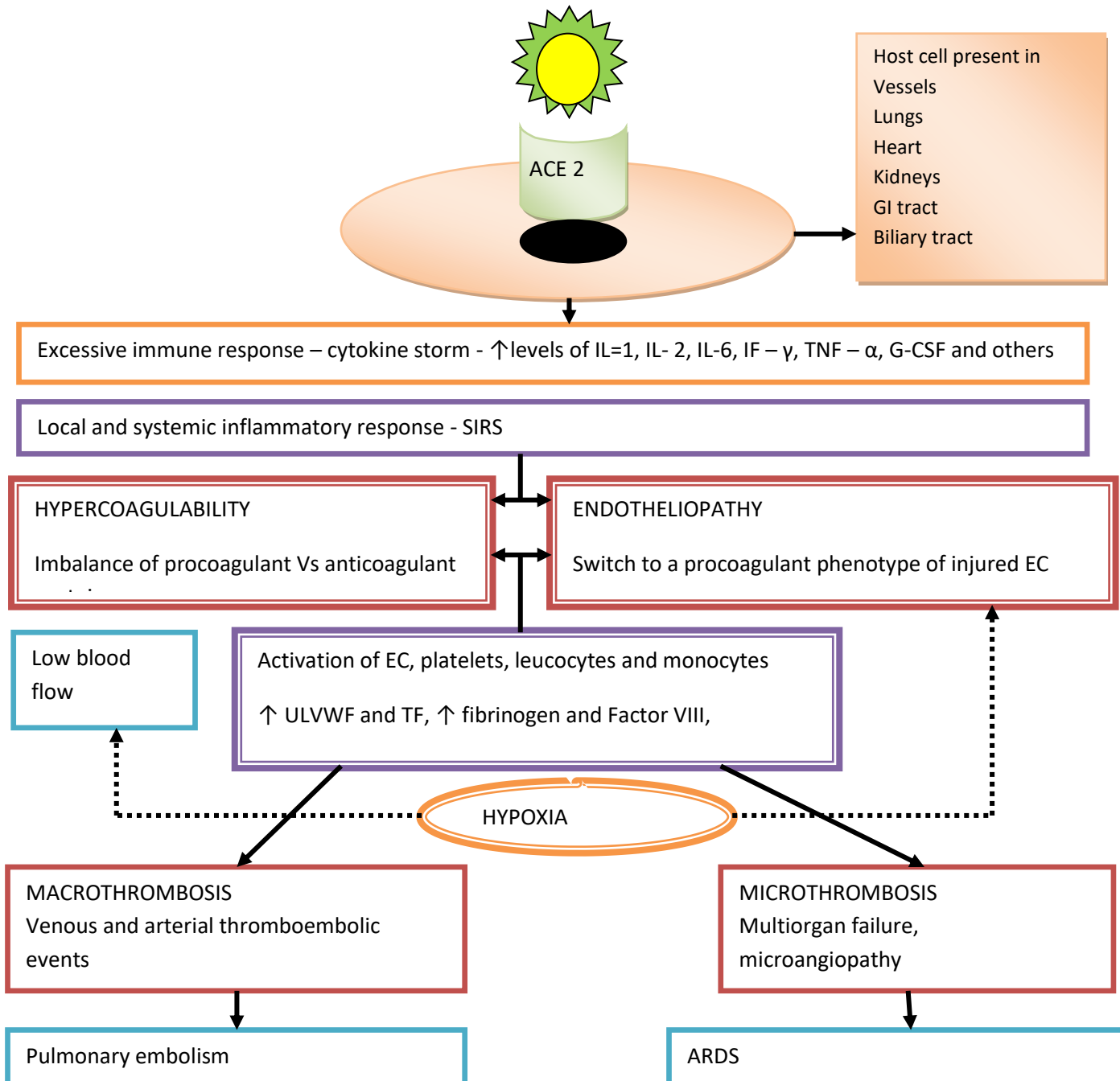
**Algorithmic approach to patients with exertional desaturation / radiological evidence of interstitial pneumonia without hypoxia at rest**



Exertional desaturation test to be considered only if saturation at rest in room air is more than 95% and patient is clinically stable. If there is fall in SPO2 by more than 3% from base line after 6 min walk test or 40 step test consider initiation of steroids. All clinically stable patients in home care should also undergo 6 minute walk test atleast once a day

## 5. ANTICOAGULATION

### PATHOGENESIS OF COVID – 19 AND THE NEED FOR ANTICOAGULATION



For COVID 19 patients with moderate to severe disease, evidence from REMAP CAP, ATTACC and ACTIV-4 A trials recommends the use of prophylactic dose anticoagulation over intermediate or higher intensity anticoagulation. Therapeutic anticoagulation should be reserved for patients with suspected or proven venous or arterial thrombosis. But with delta variant as increased risk of thrombosis has been observed, Clinical Infectious Disease Society India recommends therapeutic dose anticoagulation for moderate to severe disease.

COVID-19 contributes to a hypercoagulable state and thrombotic events are fairly common. Due to the frequency of arterial and venous thrombosis as well as micro-vascular thrombosis demonstrated on lung histology, many clinicians all over the world have opted to use therapeutic anticoagulation in patients with severe or critical illness. In addition, there are numerous reports suggesting that the delta variant (B.1.617.2), now the predominant strain circulating widely in India, results in many more thrombotic events and has also contributed to intrauterine deaths. Hence prophylactic anticoagulation is standard practice for all hospitalized patients with COVID-19. Standard prophylactic doses or Intermediate weight-adjusted doses of anticoagulation for thromboprophylaxis in hospital and ICU settings have been found to have similar safety and efficacy in preventing death or thrombosis, with a slightly higher risk of bleeding with Intermediate weight-based dosing anticoagulation. Hence with the present evidence available, guideline recommend only prophylactic dose anticoagulation in patients with mild, moderate (without hypoxia) or critical illness, though this may need to be individualized in obesity, pregnancy and renal insufficiency.

Overall among those with moderate (with hypoxia), severe and critical COVID-19 studied, therapeutic dose anticoagulation probably prevents clinically defined thrombotic events by 39% (risk ratio (RR) 0.61 (95% confidence interval (CI) 0.45 to 0.82); moderate certainty in the evidence). It may not reduce mortality, and its effect on organ support free days is uncertain. It does, however, probably improve chance of survival without organ support at 28 days by 6% (95% CI 1% to 10%; moderate certainty in the evidence).

In moderate (with hypoxia) to severe group of patients considered, the initiation of therapeutic anticoagulation led to a probable decrease in thrombotic events by 37% (95% CI 7% to 57%), probable increase in organ support free days (OSFD) by 5% (95% CI 1% to 10%), along with a probable increased risk of bleeding.

When the critical severity group was evaluated separately, therapeutic anticoagulation probably reduced thrombotic events by 43% (95% CI 11% to 63%) with probably no decrease in all-cause mortality or OSFD. In addition, there was probably no increase in bleeding (RR 1.39; 95% CI 0.71 to 2.71). Due to the increasing reports of thrombosis in all categories of patients in India, clinician discretion is advised for this critical category of patients. The advantages and disadvantages of therapeutic dose anticoagulation has to be carefully weighed. In critical it is very difficult to pick up a thrombotic event easily which may impact eventual mortality and morbidity, and it is most often based on a clinical suspicion which is often very difficult to confirm as these patients are not amenable to easy shifting for a confirmatory radiology. Compared to thrombosis, major bleeding can be



diagnosed clinically easily. In addition, fatal bleeding events, reported only by the mpRCT (non-critical) trial, were only 3 in the therapeutic dose group as compared to 1 in the non-therapeutic dose group, though the actual numbers were not reported in the critical category. Despite the uncertainty reflected in the various guidelines from NIH or NICE where due to the lack of trial data they are unable to categorically recommend therapeutic over prophylactic dose, clinicians in India are increasingly recommending an intermediate or therapeutic dose of anticoagulation in severe and critical categories. However, more trials are required to support a conclusion that therapeutic dose anticoagulation is beneficial in the critical category.

Overall therapeutic dose anticoagulation is a low-cost intervention and needs to be weighed against hospitalization and ICU care costs that may result due to a thrombotic event. In addition, clinicians need to make a judgement call regarding the balance between risk of thrombosis and the risk of bleeding in an individual patient.

## **RECOMMENDATIONS**

The guideline recommends against the use of anticoagulation in COVID-19 patients who do not require hospitalization. At least prophylactic dose anticoagulation is strongly recommended in patients who are hospitalized with COVID-19 in the moderate, severe or critical categories of COVID-19. A conditional recommendation is made for therapeutic dose anticoagulation in patients with moderate COVID-19 with hypoxia and in patients with severe COVID-19.

**IN ALL HOSPITALIZED PATIENTS IN MODERATE, SEVERE AND CRITICAL CATEGORIES:** Strong recommendation for at least prophylactic dose anticoagulation. In the mild category anticoagulation may be individualized based on risk factor assessment and standard hospital practice

**MILD ILLNESS OR MODERATE ILLNESS (WITHOUT HYPOXIA):** No recommendation for or against therapeutic dose of anticoagulation in hospitalized patients with no oxygen requirements (lack of evidence); clinicians may decide to use prophylactic dose anticoagulation based on the clinical picture (see justification and implementation considerations)

**MODERATE ILLNESS:** Conditional recommendation for therapeutic dose anticoagulation in hospitalized patients with progressively increasing oxygen requirement

SEVERE ILLNESS: Conditional recommendation for use of therapeutic dose of anticoagulation

**CRITICAL ILLNESS:** ie Requirement for high-level respiratory support: noninvasive ventilation, high-flow oxygen ( $\geq 20$  litres per minute) or invasive mechanical ventilation OR acute respiratory distress syndrome (PaO<sub>2</sub>/FiO<sub>2</sub> ratio of  $< 300$ ) OR sepsis OR shock

No recommendation for or against therapeutic anticoagulation in this category (based on insufficient evidence). Clinicians may decide to use prophylactic dose anticoagulation appropriately based on the clinical picture (see justification and implementation considerations)

Product	Thromboprophylaxis dose		Therapeutic dose
	Low dose	Intermediate dose	
Low Molecular Weight Heparin (LMWH) – (doses given for Enoxaparin)	40 mg q24h [BMI > 40/Weight > 120 Kg – dose increase to 40 mg q12h]	1 mg/kg q24h	1 mg/kg q12h
Unfractionated Heparin (UFH)	5000U q12h	5000 U q8h OR 7500 U q12h	80 U/kg bolus followed by 18 U/kg/hour infusion Targeting APTT of 55-75 seconds

**Critical illness:**

- Requirement for high-level respiratory support: noninvasive ventilation, high-flow oxygen ( $\geq 20$  litres per minute) or invasive mechanical ventilation
- OR acute respiratory distress syndrome (PaO<sub>2</sub>/FiO<sub>2</sub> ratio of  $< 300$ )
- OR sepsis
- OR shock

Overall, anticoagulation is feasible to implement widely and easily. There is evidence for injectable low molecular weight heparin and unfractionated heparin through the data presented. However, Direct Oral Anti Coagulants (DOACs) like Rivaroxaban/Apixaban are being used in COVID-19 patients widely in clinical practice. However, in our analysis they were studied only in one of the smaller trials and hence data regarding its efficacy in COVID-19 is scarce. Given the increased risk in bleeding noted and difficulty in immediate reversal of anticoagulant effect of DOACs, decision to prescribe these should weigh these benefits and harms especially when administering at therapeutic doses.

Enoxaparin achieves anticoagulant effect by activating antithrombin. Routine laboratory monitoring for efficacy is not usually necessary. However, in special situations such as obesity, renal insufficiency, and pregnancy, laboratory monitoring may be required. The peak anti-factor Xa (anti-Xa) level is the recommended test for monitoring enoxaparin efficacy. Blood samples should be withdrawn about 3–5 hours after dose administration. In patients on therapeutic anticoagulation with unfractionated heparin, APTT monitoring can be done and maintained 1.5 to 2 times the control. In other anticoagulation regimens using low molecular weight heparin or Fondaparinux, regular anti-Xa monitoring is not recommended other than in obese, pregnancy or in renal insufficiency patients. In addition, in obese patients that intermediate dose of anticoagulation may need to be considered over prophylactic dose anticoagulation to achieve the required prophylactic levels. Renal insufficiency may prompt also prompt dose modification. In pregnancy data is still evolving and decisions regarding the required dose may need to take into consideration indications other than COVID-19. In the setting that heparin resistance is suspected, even in the setting of unfractionated heparin, anti-Xa levels should be monitored. Target peak anti-Xa for the treatment doses of twice-daily enoxaparin is 0.6–1.0 IU/mL. The target peak anti-Xa level for prophylactic doses of enoxaparin is 0.2–0.5 IU/mL [22].

**The following points are to be considered prior to initiating anticoagulation in patients:**

1. Contra-indications to anticoagulation:
  - Absolute: Platelets  $<20,000/\text{mm}^3$ ,
  - Relative: platelets  $<50,000/\text{mm}^3$ ; Brain metastases; Recent major trauma; Major abdominal surgery within the past 2 days; Gastrointestinal or genitourinary bleeding within the past 14 days; Endocarditis; Severe hypertension (systolic BP  $>200$  or diastolic BP  $>120$  mmHg).
2. Specific contraindications and dosing considerations:
  - Enoxaparin: Known hypersensitivity to enoxaparin, heparin or other LMWHs; History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies; Active major bleeding and conditions with a high risk of uncontrolled haemorrhage including recent haemorrhagic stroke
  - If anticoagulant prophylaxis is contraindicated, apply sequential compression device (SCD) . SCD should not be placed if a DVT is present or there are signs/symptoms of DVT (i.e., unilateral leg swelling and pain).

<b>Prophylactic dose (Non-therapeutic) anticoagulation</b>	
Low molecular weight heparin (LMWH)	Enoxaparin 40mg Q24H (or equivalent dose of other LMWH); increase to 40mg Q12H if BMI >40 or weight >120 kg / m <sup>2</sup>
Unfractionated heparin (UFH)	5000 Units s/c Q12H or Q 8hrly 7500 Units s/c Q 12hrly if BMI > 40 kg/m <sup>2</sup>
Apixaban	2.5mg BD
Rivaroxaban	10mg OD
Fondaparinaux	2.5mg s/c OD
Dalteparin	5000 Units s/c OD

<b>Therapeutic dose anticoagulation</b>	
Low molecular weight heparin (LMWH)	Enoxaparin 1mg/kg Q12H (or equivalent dose of another LMWH) if creatinine clearance > 30ml/min Enoxaparin 1mg/kg Q 24 hrly if creatinine clearance <30ml/min (UFH preferred)
Unfractionated heparin (UFH)	80 U/kg bolus, followed by 18 U/kg/hr infusion [Targeting APTT of 55-75 seconds]
Apixaban	5mg BD / 10mg BD
Rivaroxaban	15-20mg OD
Fondaparinaux	5mg s/c OD if weight < 50 Kg 7.5 Mg OD if weight between 50 and 100 Kg 10mg OD if weight > 100 Kg
Dalteparin	100 units / kg S/c Q 12hly if creatinine clearance > 30ml/min

*Reference :American society of haematology 2021 guidelines on the use of anticoagulation for patients with COVID 19*

**Post Discharge thrombo-prophylaxis**

Should be restricted to patients with COVID -19 patients

1. Modified International Medical prevention registry on Venous Thromboembolism (Improve) VTE risk  $\geq 4$ ; or
2. Modified IMPROVE VTE risk score  $\geq 2$  and D-Dimer level  $\geq 2$  times the upper limit of normal

**The Improve risk assessment model (modified IMPROVE VTE risk score)**

Risk Factor	
Prior venous thromboembolism	3
Diagnosed thrombophilia	2
Current lower limb paralysis	2
Current cancer	2
Immobilized for atleast 7 days	1
Stay in the ICU or coronary care unit	1
More than 60 yrs old	1

Post discharge VTE prophylaxis either Tab Apixaban 2.5mg BD or Tab Rivoraxaban 10mg OD for a period of 2-3 weeks may be considered.

Modified IMPROVE VTE risk score  $< 2$  and D-Dimer level  $\geq 2$  times the upper limit of normal –Tab Ecospirin 75mg OD for 2-3 weeks may be considered

**When to suspect Pulmonary Embolism:**

This is a challenge given the inherent hypoxia and altered coagulation profile observed in COVID-19 infected patients.

Consider PE in the case of:

- a. Marked increase/rising D-dimer from baseline AND
- b. Acute worsening of oxygenation, blood pressure, tachycardia with imaging findings **NOT** consistent with worsening COVID-19 Pneumonia.

**Rationale for early anti coagulation**

- Pathophysiology of COVID – 19 associated respiratory disease is consistent with pulmonary vascular thromboemboli with increased dead space ventilation

- Autopsy studies have demonstrated venous thrombo-embolism in deceased COVID-19 patients
- Early anticoagulation is necessary to prevent propagation of micro thrombi at disease presentation
- Early anticoagulation may be associated with decreased mortality

#### **Rationale for choice of Anticoagulant**

- Heparin binds tightly to COVID - 19 spike protein
- Heparin also downregulate IL-6 and directly dampen immune activation

#### *References*

1. India covid clinical guidelines-anticoagulation: CIDS
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3. Massachusetts General Hospital Hematology Recommendations and Dosing Guidelines during COVID-19
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## 6. REMDESIVIR

Remdesivir is an intravenous (IV) investigational nucleotide prodrug of an adenosine analog. Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. It has demonstrated *in vitro* activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1</sup> In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.<sup>2</sup>

Remdesivir has been studied in several clinical trials for the treatment of COVID-19. The recommendations for use of Remdesivir is based on the results of these trials

### **Recommendation for Prioritizing Limited Supplies of Remdesivir**

- Since supplies are limited, remdesivir should be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

### **Recommendation for Patients with COVID-19 Who Are on Supplemental Oxygen but Who Do Not Require High-Flow Oxygen, Noninvasive or Invasive Mechanical Ventilation, or ECMO**

- Use **remdesivir** for 5 days or until hospital discharge, whichever comes first. If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

### **Recommendation for Patients with COVID-19 Who Require High-Flow Oxygen, Noninvasive Ventilation, Mechanical Ventilation, or ECMO**

- There is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, so a recommendation either for or against starting remdesivir. Cannot be made based on the available evidence till now.

In a randomized clinical trial, there was no observed difference between the remdesivir and placebo groups in time to recovery or mortality rate in these subgroups. However, because the trial was not powered to detect differences in outcomes in these subgroups, there is uncertainty as to the effect of remdesivir on the course of COVID-19 in these patients.

### **Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy**

- There are insufficient data on the optimal duration of remdesivir therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some experts extend the total remdesivir treatment duration to up to 10 days.

### *Rationale*

The recommendations for remdesivir are largely based on data from a multinational, randomized, placebo-controlled trial (the Adaptive COVID-19 Treatment Trial [ACTT]). This trial included 1,063 hospitalized patients with COVID-19 and evidence of lower respiratory tract infection who received IV remdesivir or placebo for 10 days (or until hospital discharge, whichever came first).

Participants who received remdesivir had a shorter time to clinical recovery than those who received placebo (median recovery time of 11 days vs. 15 days, respectively). In the preliminary subgroup analyses of ACTT, there was no observed benefit for remdesivir in people with COVID-19 who did not require oxygen supplementation; however, the number of people in this category was relatively small. Remdesivir is being evaluated in another clinical trial for the treatment of patients with moderate COVID-19; complete data from this trial are expected soon.

The preliminary analysis also reported that the patients with the clearest evidence of clinical benefit from starting remdesivir were those who required supplemental oxygen but who did not require high-flow oxygen, noninvasive or mechanical ventilation, or ECMO at baseline (n = 421). In this subgroup, those who received remdesivir had a shorter time to recovery than those who received placebo (recovery rate ratio 1.47; 95% confidence interval [CI], 1.17–1.84); in a post-hoc analysis of deaths by Day 14, remdesivir appeared to confer a survival benefit (hazard ratio [HR] for death 0.22; 95% CI, 0.08–0.58).

In patients who required high-flow oxygen or noninvasive ventilation at baseline (n = 197), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.20; 95% CI, 0.79–1.81). In the post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.12; 95% CI, 0.53–2.38).

In participants who were on mechanical ventilation or ECMO at baseline (n = 272), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.95; 95% CI, 0.64–1.42). In the post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.06; 95% CI, 0.59–1.92).

A review of the final data set, which included 28-day mortality, showed that this data set was consistent with the published preliminary data (unpublished data, based on communication from the ACTT study team to the Panel).

For patients with COVID-19 who required high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, there was no observed difference between the remdesivir and placebo groups in time to recovery or mortality rate. However, because the trial was not powered to detect differences in outcomes within these subgroups, there is uncertainty as to whether starting remdesivir confers clinical benefit in these patients. For this reason, a recommendation cannot be made either for or against starting remdesivir in these patients. Because the supply of remdesivir is limited, the drug should be prioritized for use in those in whom efficacy has been demonstrated (i.e., in hospitalized patients who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO).



Data from a multinational, open-label trial of hospitalized patients with severe COVID-19 showed that remdesivir treatment for 5 or 10 days had similar clinical benefit. The optimal duration of therapy for patients who do not improve after 5 days of receiving remdesivir is unclear. In the absence of data, some experts consider extending the total treatment duration of remdesivir to up to 10 days in patients who do not improve after 5 days of remdesivir.

#### *Monitoring, Adverse Effects, and Drug-Drug Interactions*

Remdesivir can cause gastrointestinal symptoms (e.g., nausea, vomiting), elevated transaminase levels, and an increase in prothrombin time (without a change in the international normalized ratio).

Clinical drug-drug interaction studies of remdesivir have not been conducted. Remdesivir levels are unlikely to be substantially altered by cytochrome P450 (CYP) 2C8, CYP2D6, or CYP3A4 enzymes, or by P-glycoprotein (P-gp) or organic anion-transporting polypeptide (OATP) drug transporters.

Remdesivir may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP, or P-gp. Strong induction may modestly reduce remdesivir levels. The clinical relevance of lower remdesivir levels is unknown. The use of remdesivir with strong inducers (e.g., rifampin) **is not recommended**.

Minimal to no reduction in remdesivir exposure is expected when remdesivir is co-administered with dexamethasone. Chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.

Because the remdesivir formulation contains renally cleared sulfobutylether-beta-cyclodextrin sodium, it is contraindicated in patients with creatinine clearance  $<30\text{ml/min/m}^2$

#### Considerations in Pregnancy

- Use remdesivir in pregnant patients only when the potential benefit justifies the potential risk to the mother and the fetus. It should be considered in pregnancy only on compassionate grounds after getting consent from the state medical board.
- The safety and effectiveness of remdesivir for treatment of COVID-19 have not been evaluated in pregnant patients.
- Remdesivir is available through the Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for adults and children and through compassionate use programs for pregnant women and children with COVID-19.

#### Considerations in Children

- The safety and effectiveness of remdesivir for treatment of COVID-19 have not been evaluated in pediatric patients.
- Remdesivir is available through an FDA EUA for adults and children and through compassionate use programs for children with COVID-19. A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (*ClinicalTrials.gov* identifier NCT04431453).

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## 7. Available evidence on the use of Tocilizumab in COVID-19

Tocilizumab is a recombinant humanized monoclonal antibody against IL-6 receptor. The indications for use of Tocilizumab have been modified based on the RECOVERY and REMAP-CAP trials. WHO considered data from over 10000 patients enrolled in 27 clinical trials and found that tocilizumab reduce odds of death by 13%.The odds of mechanical ventilation among severe and critical patients are reduced by 28% compared with standard care.

### Rationale for use of Tocilizumab in COVID-19

Pro-inflammatory cytokine levels are elevated in COVID-19 infection. Predictors of mortality from a retrospective, multi-centre study of 150 confirmed COVID-19 cases in Wuhan, China included elevated ferritin and IL-6. This suggests that virus induced hyper inflammation is contributing to the mortality<sup>1,2</sup>.

Tocilizumab has been found useful in severe or life-threatening cases of cytokine release syndrome (CRS) due to chimeric antigen receptor-T cell therapy. However, there are no randomized control trials that compared Tocilizumab versus steroids for CRS<sup>3</sup>.

### Dose recommended for CRS:

>18 years: 8mg/kg IV (400mg),

< 18 years:

< 30kg: 12mg/kg IV over 60 minutes

>30kg: 8mg/kg (max 800mg) IV over 60minutes

The total tocilizumab dose should not exceed 800 mg<sup>4</sup>.

If no effect can repeat x 1 more dose after 8 to 12 hours

Can be given as an intravenous infusion in normal saline over 1 hour.

### Dose modification of Tocilizumab in case of liver enzyme derangement

Liver enzymes 1-3 times upper limit of normal	For patients receiving intravenous Tocilizumab, reduce dose to 4 mg per kg or hold the drug until ALT or AST have normalized
Liver enzymes 3-5 times upper limit of normal	Hold Tocilizumab dosing until less than three times upper limit of normal and follow recommendations above for greater than 1 to three times upper limit of normal For persistent increases greater than three times upper limit of normal, discontinue
Liver enzymes > 5 times upper limit of normal	Discontinue the drug

### Drug dosing based on Absolute Neutrophil Count and Platelet Count

Lab Parameter (cells/mm <sup>3</sup> )	Recommendation
ANC > 1000	Maintain drug dose
ANC 500- 1000	Hold Tocilizumab dosing When ANC greater than 1000 cells per mm <sup>3</sup> : <ul style="list-style-type: none"> <li>• For patients receiving intravenous drug, resume Tocilizumab at 4 mg per kg and increase to 8 mg per kg as clinically appropriate</li> <li>• For patients receiving subcutaneous tocilizumab, resume drug at every other week and increase frequency to every week as clinically appropriate</li> </ul>
ANC less than 500	Discontinue the drug
Platelet count 50,000 – 1,00,000	Hold Tocilizumab dosing When platelet count is greater than 100,000 cells per mm <sup>3</sup> : <ul style="list-style-type: none"> <li>• For patients receiving intravenous drug, resume Tocilizumab at 4 mg per kg and increase to 8 mg per kg as clinically appropriate .</li> </ul>
Platelet count < 50,000	Discontinue Tocilizumab

### Guidelines and recommendations:

<b>TOCILIZUMAB</b>
<p>When all below categories are met</p> <ul style="list-style-type: none"> <li>• Severe disease (preferably within 24 – 48 hours of onset of severe disease / ICU admission)</li> <li>• Significantly Raised inflammatory markers CRP &amp;/or IL-6 (RECOVERY TRIAL cut off &gt; 75mg/L)</li> <li>• Not improving despite use of steroids</li> <li>• No active bacterial / fungal / tubercular infection</li> <li>• Recommended dose is 4-6ml/kg (usually a dose of 400mg in a 60Kg adult) in 100ml NS over 1 hour (Single Dose)</li> </ul>

## References:

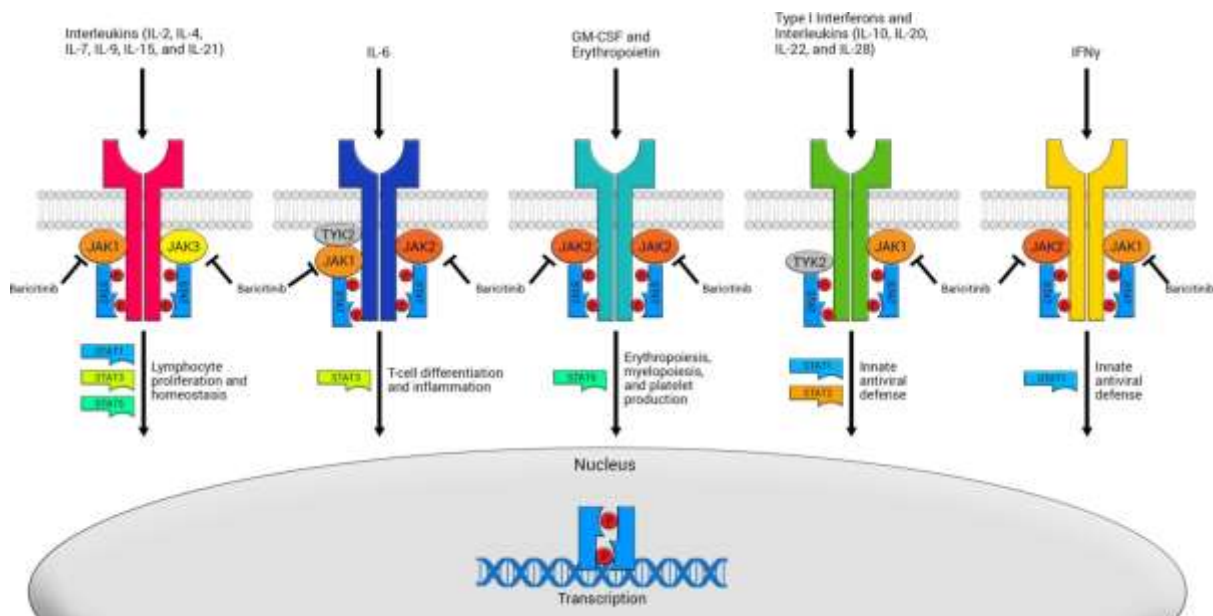
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## 8. Janus Kinase Inhibitors- Baricitinib and Tofacitinib

The Janus kinase inhibitors like baricitinib and tofacitinib can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6). Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins that are involved in vital cellular functions, including signaling, growth, and survival. The proinflammatory cytokine IL-6 acts mainly through JAK/STAT pathway which can be blocked by JAK inhibitors. All JAK inhibitors block different types of JAK receptors JAK 1, 2, 3 and TyK 2.

Immunosuppression induced by this class of drugs may potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19. Baricitinib administration resulted in a dose dependent inhibition of IL-6 induced STAT3 phosphorylation in whole blood from healthy subjects with maximal inhibition observed approximately 1 hour after dosing, which returned to near baseline by 24 hours.

Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral clathrin mediated endocytosis, potentially preventing entry of virus into and infection of susceptible cells.



Severe manifestations of SARS-CoV-2 infection are associated with an exaggerated immune response driven by interleukin-6, tumour necrosis factor  $\alpha$ , and other cytokines in a pattern referred to as cytokine storm. Tofacitinib is an orally administered selective inhibitor of Janus kinase (JAK) 1 and JAK 3, with functional selectivity for JAK 2, that blocks intracellular transduction pathways after a cytokine is bound to its receptor. As a

consequence, no cellular response is triggered, and cytokine production is indirectly suppressed. Tofacitinib also modulates the action of interferons and interleukin-6, decreasing the release of cytokines by type 1 and type 17 helper T cells, which are implicated in the pathogenesis of the acute respiratory distress syndrome. Thus, the action of tofacitinib on multiple critical pathways of the inflammatory cascade may ameliorate progressive, inflammation-driven lung injury in hospitalized patients with Covid-19.

Recommendations for the use of baricitinib are based on data from the Adaptive COVID-19 Treatment Trial 2 (ACTT-2), a multinational, randomized, placebo-controlled trial of baricitinib use in hospitalized patients with COVID-19 pneumonia. Participants (n = 1,033) were randomized 1:1 to oral baricitinib 4 mg or placebo, for up to 14 days, in combination with intravenous (IV) remdesivir, for up to 10 days. Participants who received baricitinib had a shorter time to clinical recovery than those who received placebo (median recovery time of 7 vs. 8 days, respectively). This treatment effect was most pronounced among those who required high-flow oxygen or non-invasive ventilation but were not on invasive mechanical ventilation. The difference in mortality between the treatment groups was not statistically significant.

Recently in the STOP-COVID trial, the efficacy and safety of Tofacitinib was assessed in patients hospitalised due to COVID 19 pneumonia. The study randomly assigned, in a 1:1 ratio, hospitalized adults with Covid-19 pneumonia to receive either tofacitinib at a dose of 10 mg or placebo twice daily for up to 14 days or until hospital discharge. The primary outcome was the occurrence of death or respiratory failure through day 28 as assessed with the use of an eight-level ordinal scale (with scores ranging from 1 to 8 and higher scores indicating a worse condition). The cumulative incidence of death or respiratory failure through day 28 was 18.1% in the tofacitinib group and 29.0% in the placebo group (risk ratio, 0.63; 95% confidence interval [CI], 0.41 to 0.97; P=0.04). Death from any cause through day 28 occurred in 2.8% of the patients in the tofacitinib group and in 5.5% of those in the placebo group (hazard ratio, 0.49; 95% CI, 0.15 to 1.63). The proportional odds of having a worse score on the eight-level ordinal scale with tofacitinib, as compared with placebo, was 0.60 (95% CI, 0.36 to 1.00) at day 14 and 0.54 (95% CI, 0.27 to 1.06) at day 28. Serious adverse events occurred in 20 patients (14.1%) in the tofacitinib group and in 17 (12.0%) in the placebo group. The STOP-COVID trial showed that among patients hospitalized with Covid-19 pneumonia, tofacitinib led to a lower risk of death or respiratory failure through day 28 than placebo.

The results of ACTT-2 and STOP-COVID provide evidence that JAK inhibition represents an additional therapeutic option for treating Covid-19 pneumonia in patients who are not yet receiving invasive mechanical ventilation. These agents are orally administered and have few drug–drug interactions.

The role of baricitinib and tofacitinib in the treatment of COVID-19 is evolving and reserved only for emergency use with the approval of Institutional Medical Board.

## Indications for JAK inhibitors in COVID 19

Diagnosed COVID 19 infection

1. Consider only for patients who have not received Tocilizumab or on mechanical ventilation, who require 8 L O<sub>2</sub> or FiO<sub>2</sub> > 0.4 or higher levels of respiratory support for at least 8 hours and are not improving despite 24 hours of standard care including dexamethasone.
2. In rare circumstance when corticosteroids cannot be used, **baricitinib** or tofacitinib **may be used** for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation.

Baricitinib or tofacitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Dose: Baricitinib - Oral 4 mg once daily

Tofacitinib – Oral 10 mg twice a day.

Duration of baricitinib and tofacitinib is 7 to 14 days based on clinical response or until hospital discharge.

**Patients must have an eGFR, aminotransferases, and CBC with differential determined prior to first administration of baricitinib or tofacitinib**

## Contraindications

1. In patients with an absolute lymphocyte count <500 cells/mm<sup>3</sup>, absolute neutrophil count <1,000 cells/mm<sup>3</sup>, or hemoglobin <8 g/dL.
2. Active serious infections including localized infections.
3. Avoid in active Tuberculosis.
4. Should not combine with potent immunosuppressants like Tocilizumab, cyclosporine, azathioprine etc
5. Pregnancy and lactation
6. Patients who are on dialysis or have end-stage renal disease (ESRD, EGFR <15 mL/minute/1.73 m<sup>2</sup>)
7. Tofacitinib may lead to PR interval prolongation so use with caution in patients with heart rate < 60 beats per minute, conduction abnormalities, syncope, arrhythmias, ischaemic heart disease or heart failure.



**Dosing of Baricitinib in renal impairment:**

- eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>: No dose adjustment
- eGFR 30 to  $<60$  mL/min/1.73 m<sup>2</sup>: Decrease to 2 mg/day
- eGFR 15 to  $<30$  mL/min/1.73 m<sup>2</sup>: Decrease to 1 mg/day
- eGFR  $<15$  mL/min/1.73 m<sup>2</sup>, patients on dialysis, have end-stage renal disease, or have acute kidney injury: Not recommended

**Dosing of Tofacitinib in renal impairment:**

- Mild impairment: No dose adjustment
- Moderate to severe impairment: reduce dose to 5mg twice daily (if taking 10mg twice daily).
- ESRD: Administer after dialysis session on dialysis days; if dose given prior to dialysis, supplemental dose is not recommended after dialysis session. Reduce dose to 5mg twice daily (if taking 10mg twice daily).

**Dosing in Hepatic Impairment:****Baricitinib**

- Mild to moderate: No dosage adjustment necessary.
- Severe: Use is not recommended (has not been studied). Use only if benefits outweigh risks.
- Hepatotoxicity during therapy (increases in ALT or AST): Discontinue baricitinib until drug-induced liver injury is excluded.

**Tofacitinib**

Mild impairment no adjustment necessary

Moderate impairment: reduce dose to 5mg twice daily (if taking 10mg twice daily) or 5mg once daily (if taking 5mg twice daily)

Severe impairment: use not recommended

**Administration:**

Orally, May be administered with or without food.

Alternatively, the tablet may be dispersed in a small amount (5 to 10 mL) of liquid (water, whole milk); the tablet will disperse in  $<5$  minutes.

**Adverse reactions: Any adverse reaction needs close monitoring. Important ones described with JAK inhibitors are:**

1. Hypersensitivity
2. Serious Infections including bacterial,viral,invasive fungal, and other opportunistic infections have been reported. If serious infections are suspected JAK inhibitors should be discontinued immediately.
3. Arterial and venous thrombosis including pulmonary embolism.
4. Elevation of ALT/AST
5. GI perforation-eventhough exact cause is not known, JAK inhibitors should be used with caution in patients at risk of perforation like those with diverticulitis.
6. Reactivation of herpes zoster. [1.5 to 2 fold higher than in general population] and herpes simplex.
7. CPK elevation-as proinflammatory cytokines can block differentiation of myoblasts into mature myocytes.
8. Baricitinib: Thrombocytosis-platelet count increase rapidly after initiation and peak around week 2 [mean increase  $50 \times 10^9/L$ ]. This is due to selective JAK-2 inhibition leading to thrombopoetin elevation.
9. Tofacitinib: may cause thrombocytopenia

If any adverse reaction suspected, stop therapy and evaluate.

### **Drug interactions:**

#### **Baricitinib**

Coadministration with strong organic anion transporter 3 (OAT3) inhibitors (eg, probenecid)

- If recommended dose is 4 mg/day, reduce to 2 mg/day

#### **Tofacitinib**

- Dose should be reduced when used with strong CYP 3 A 4 inhibitors (eg Ketoconazole) or CYP 2C19 inhibitors (Fluconazole)
- Should not be co-administered with strong CYP 3A4 inhibitors like Rifampicin

**Baricitinib and Tofacitinib should not be administered in patients who have received Tocilizumab**

### References

- 1.NIH COVID 19 Treatment Guidelines-Kinase inhibitors: Baricitinib and other JAK inhibitors.
- 2.Baricitinib: A review of pharmacology, safety and Emerging Clinical Experience in COVID 19 :Sarah Jorgensen et al:Pharmacotherapy Vol 40:2020
- 3.Tofacitinib in Patients Hospitalised with Covid-19 Pneumonia: Patricia .O.Guimaraes et al: NEJM Jun 16,2021

## 9. TECHNICAL GUIDELINES REGARDING USE OF – CASIRIVIMAB AND IMDEVIMAB

Monoclonal antibodies (mAbs) are a set of identical antibodies that have high specificity and affinity for a single epitope. They have been demonstrated to be safe and effective in selected viral diseases when used for prophylaxis (respiratory syncytial virus) or treatment (Ebola virus disease). The clinical efficacy of mAbs in viral infections is thought to be mediated through direct binding to free virus particles and neutralisation of their ability to infect host cells. mAbs may also bind to viral antigens expressed on the surface of infected cells and stimulate antibody-dependent phagocytosis and cytotoxicity via the Fc portion of the mAb.

SARS-CoV-2 infection is initiated by binding of the viral transmembrane spike glycoprotein to angiotensin converting enzyme 2 (ACE2) on the surface of host cells. The receptor binding domain of the spike glycoprotein is, consequently, the main target for neutralising antibodies. Following the emergence of SARS-COV-2, mAbs targeting the spike receptor binding domain were rapidly isolated from humanised mice and from peripheral B cells of recovered patients. Anti-SARS-CoV-2 spike protein neutralizing mAbs have demonstrated in vivo efficacy in both therapeutic and prophylactic settings in mouse, and non-human primates models, with decrease in viral load and lung pathology.

US FDA, EMA and CDSCO has given EUA for two high-affinity human IgG1 anti-SARS-CoV-2 mAbs, casirivimab and imdevimab, which bind specifically to the receptor binding domain of the spike glycoprotein of SARS-CoV-2, blocking viral entry into host cells. A combination of antibodies that bind to non-overlapping epitopes, rather than a single antibody, is intended to minimize the likelihood of loss of antiviral activity due to naturally circulating viral variants or development of escape mutants under drug pressure. In a clinical study in non-hospitalised adults with SARS-COV-2 infection and risk factors for severe COVID- 19, the combination of casirivimab and imdevimab (REGEN-COV) was safe and, compared to placebo, reduced virus load in the upper airway, shortened the time to symptom resolution, and reduced the composite outcome of COVID-19-related hospitalisation or all-cause mortality.

### **High-Risk Criteria in the Emergency Use Authorizations for Anti-SARS-CoV-2 Monoclonal Antibodies**

Casirivimab and imdevimab should be administered only after getting approval of institutional medical board. An informed written consent must be obtained from all patients. Inorder to justify the NNT to prevent progression to severe disease, patient selection should be based on the following high risk factors.

#### High-risk individuals who will benefit from Monoclonal antibody cocktail

- Body mass index (BMI)  $\geq 35$
- Chronic kidney disease stage with eGFR $<60$ ml/min especially in those on MHD.
- Diabetes mellitus [HBA1C  $>10$ ] or diabetes with end organ damage.
- Chronic liver disease
- Immunocompromising conditions.
- Currently receiving immunosuppressive treatment
- Age  $\geq 65$  years
- Cardiovascular disease
- Chronic respiratory diseases.
- Malignancies with chance of survival.
- Other indications as deemed fit by institutional medical board.

In those between 12 to 17 years with BMI  $\geq 85$ th percentile for their age and gender Mab cocktail may be considered in

- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders (e.g., cerebral palsy)
- A medical-related technological dependence that is not related to COVID-19 (e.g., tracheostomy, gastrostomy, positive pressure ventilation)
- Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control.

#### **CONTRAINDICATIONS**

Aim of administration of anti-SARS-COV-2 monoclonal antibodies is to prevent disease progression. So it has to be administered early in the disease course before hypoxia develops. It should NOT BE administered in

1. Those who require oxygen therapy due to COVID-19; or
2. Those who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and, because of COVID-19, require an increase in oxygen flow rate from baseline.
3. More than 10 days from symptom onset.

#### **Dosage:**

The approved dosage in India by CDSCO for adults and in pediatric patients (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion over at least 60 minutes or administered subcutaneously. Casirivimab and imdevimab solutions must be diluted prior to administration. Casirivimab and imdevimab should be given together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

## **Preparation and Administration**

Preparation Casirivimab and imdevimab are each supplied in individual single-dose vials. Casirivimab and imdevimab solutions must be diluted prior to administration. Casirivimab and imdevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat. Do not shake the vials.
2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded, and fresh solution prepared. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow
3. Obtain an IV infusion bag containing 250 mL of 0.9% Sodium Chloride Injection.
4. Withdraw 5 mL of casirivimab and 5 mL of imdevimab from each respective vial using two separate syringes and dilute together in the infusion bag containing 0.9% Sodium Chloride Injection.
5. Gently invert infusion bag by hand approximately 10 times to mix. Do not shake. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours and at room temperature up to 25°C (77°F) for no more than 4 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

## **Administration**

- Casirivimab and imdevimab infusion solution should be administered by a qualified healthcare professional using aseptic technique.
- Gather the recommended materials for infusion: Polyvinyl chloride (PVC), Polyethylene (PE)-lined PVC, or Polyurethane (PU) infusion set
- In-line or add-on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer as an IV infusion via pump or gravity over at least 60 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter

- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- After infusion is complete, flush with 0.9% Sodium Chloride Injection.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

## Storage

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the individual original carton to protect from light. Do NOT freeze, shake, or expose to direct light.

### Pregnancy

#### Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Casirivimab and imdevimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. Nonclinical reproductive toxicity studies have not been conducted with casirivimab and imdevimab. In a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues, no binding of clinical concern was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing fetus. In high risk pregnancies institutional medical board can take the decision to administer casirivimab and imdevimab after obtaining informed consent.

#### Renal Impairment

Casirivimab and imdevimab are not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of casirivimab and imdevimab.

#### Hepatic Impairment

The effect of hepatic impairment on PK of casirivimab and imdevimab is unknown

## ADVERSE EVENTS

The known adverse event to casirivimab and imdevimab is hypersensitivity and infusion **reaction** and hence it should be administered under close medical supervision only. According to the EUA fact sheet for casirivimab plus imdevimab, among the 533 participants who received casirivimab plus imdevimab in the R10933-10987-COV-2067 trial, one participant had an anaphylaxis reaction that required treatment with epinephrine.

## Monitoring

- These anti-SARS-CoV-2 monoclonal antibodies are to be given as intravenous infusions and should only be administered in health care settings by qualified health care providers who have immediate access to medications to treat severe infusion reactions and to emergency medical services.
- Patients should be monitored during the infusion and for at least 1 hour after the infusion is completed.
- No dosage adjustments are required for body weight, renal impairment, or mild hepatic impairment.

### Vaccination

- SARS-CoV-2 vaccination should be deferred for  $\geq 90$  days in people who have received anti-SARS-CoV-2 monoclonal antibodies. This is a precautionary measure, as the antibody treatment may interfere with vaccine-induced immune responses.
- For people who develop COVID-19 after receiving SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.

## 10. Adult critical care guidelines

### I. CASE DEFINITION - CRITICAL

1. Respiratory failure, requiring Mechanical ventilation ( $\text{PaO}_2 < 60$  with  $\text{FiO}_2 > 0.5$  with or without  $\text{PaCO}_2 > 50$  mmHg with  $\text{pH} < 7.25$ )
2. Shock
3. Other organ failure requiring ICU admission

### II. SEVERE & CRITICAL CASE: MANAGEMENT

#### 1. Assess:

- a. General: PR, HR, BP, Respiratory Rate,  $\text{SpO}_2$ , Work of breathing
- b.  $\text{SpO}_2$
- c. Tidal volume generated if on NIV
- d. Level of consciousness
- e. Organ function
- f. System examination
- g. Screening echo
- h. Labs:
  - i. BRE: Hb, TC, DC, Platelet count
  - ii. URE
  - iii. LFT
  - iv. RFT
  - v. Lactate
  - vi. Blood sugar
  - vii. CRP
  - viii. Procalcitonin
  - ix. Coagulation profile
  - x. Ferritin, LDH
  - xi. ECG
  - xii. hsTrop T/ Trop I
  - xiii. Chest Imaging
  - xiv. NTProBNP

2. **Warning Indicators:** Increasing work of breathing, progressive decrease of peripheral Absolute lymphocyte count, increasing levels of IL-6/ C-reactive protein, Tissue oxygenation indices decreases, Lactate level increasing progressively, Chest CT/Xray shows obvious progression of lung lesions, no improvement in distress with non-invasive ventilation.



3. COVID-19 patients appear to have **two phenotypes**, from the perspective of ICU management (Gattinoni et al, 2020). Management should be optimised for each individual patient as clinically indicated, based on established strategies for the management of ARDS.

#### **L-phenotype**

- a. Typical of early presentation viral pneumonitis
- b. Hypoxaemia with preserved CO<sub>2</sub> clearance (Type 1 respiratory failure)
- c. Low Elastance (i.e. high compliance)
- d. Low V/Q matching (possibly due to abnormal hypoxic vasoconstriction)
- e. Low recruitability (poor response to PEEP and prone position ventilation)
- f. May be able to avoid mechanical ventilation with appropriate oxygen therapy

#### **H phenotype**

- a. Typical of later illness and classic ARDS, including patients who have had prolonged non-invasive ventilation (potential for patient-induced lung injury) and co-existing lung disease or complications
- b. Hypoxaemia +/- impaired CO<sub>2</sub> clearance (Type 1 and/or 2 respiratory failure)
- c. High Elastance (i.e. low compliance)
- d. High V/Q matching
- e. High recruitability (respond to PEEP and prone position ventilation)
- f. May benefit from protective lung ventilation and usual ARDS therapies.

### **4. Treatment**

- a. General Principle: Bed rest, maintain fluid balance, acid base, oxygen therapy, mechanical ventilation in time, prevent & treat complications of critically ill, treat disease, prevent secondary infections, prevent transmission.
- b. Antiviral treatment: as per state guidelines
- c. Oxygen therapy & respiratory support

#### **i. PaO<sub>2</sub>/FiO<sub>2</sub> at 200-300**

1. Nasal cannula /oxygen mask. Assess if respiratory disease/hypoxemia has remitted. If no improvement in 1-2 hours—go to next step/invasive mechanical ventilation
2. High flow nasal cannula HFNC: **limited recommendation**. If used patient ideally in Negative pressure room or single isolation room with good ventilation. More aerosol formation. Maximum for 2 hours. Close observation is needed. If no improvement /response (Respiratory Rate >35/min SpO<sub>2</sub><93%, increased work of breathing, accessory muscle use)- consider intubation and mechanical ventilation. Oxygen flow meters with flows as high as 60 Lpm needed for high FiO<sub>2</sub>.

## ii. PaO<sub>2</sub>/FiO<sub>2</sub> at 150-200

1. Non-invasive ventilation (NIV): **Limited use, more aerosols.** In Negative pressure room or single isolation room with good ventilation. When using NIV, double circuit NIV with oronasal/helmet interface, non-vented mask preferred. Use HEPA filter at expiratory limb & HMEF at Y connector. Failure rate is high, close monitoring required. If no improvement in 1-2 Hours invasive mechanical ventilation initiated promptly. Monitor for “no improvement” or worsening (Respiratory Rate >35/min SpO<sub>2</sub><93%, accessory muscle use, generating large tidal volume >9-9.5ml/kg).

## iii. PaO<sub>2</sub>/FiO<sub>2</sub><150

1. Invasive mechanical ventilation
  - a. Early appropriate mechanical ventilation
  - b. Lung protective strategy (P plateau <30, Driving Pressure <15 cms H<sub>2</sub>O). Tidal Volume 4-8 ml/kg predicted body weight (PBW). Permissive hypercapnia may be permitted to reduce volutrauma. The initial tidal volume is 6 mL/kg PBW; tidal volume up to 8 mL/kg PBW is allowed if undesirable side effects occur (e.g. dyssynchrony, pH < 7.15) and also for L phenotype with CO<sub>2</sub> retention.
  - c. Ards.net guidelines to be followed especially for H phenotype,
  - d. PEEP: Gradual increase in increments of 2, with hemodynamic monitoring. Other options include: Optimal PEEP via static compliance method/ FiO<sub>2</sub>/PEEP table in ARDS.net guideline
  - e. Neuro muscular blockade: to be considered in the setting of worsening hypoxia or hypercapnia and in situations where the patient's respiratory drive cannot be managed with sedation alone resulting in ventilator dyssynchrony and lung decruitment.
  - f. Lung recruitment: Although current evidence does not support the routine use of recruitment manoeuvres in non-COVID-19 ARDS, they could be considered in COVID-19 patients on a case by case basis. COVID-19 patients may respond well to these interventions and their application may be appropriate where the patient has not responded to other interventions. They should only be provided by clinicians experienced in undertaking these manoeuvres, dealing with their potential complications and using a closed system. Methods: See below.
  - g. Prone position Ventilation: EARLY prone ventilation may be considered for refractory hypoxemia. Effective in improving hypoxia associated with COVID-19 H phenotype. This should be done in patients with refractory hypoxemia and not improving with standard lung protective ventilation strategy and policies should include suitable PPE for staff,

minimise the risk of adverse events, e.g. accidental extubation. Muscle relaxants/deep sedation be used while ventilating in prone position to avoid accidental displacement or extubation. First session of Prone ventilation is to at least 12 hours and further sessions much longer. Usefulness of prone position ventilation is shown by P/F >150, PEEP decreasing to <10, FiO<sub>2</sub> decreasing to <0.6 after turning patient supine and that too lasting >4 Hrs

- h. Fluid Management: Conservative fluid strategy to reduce extra vascular lung water.
- i. Tracheostomy: Is an aerosolization procedure and so decide on clinical basis
- j. Nebulisers: MDI preferred over nebulisers
- k. Bronchoscopy: Diagnostic bronchoscopy is to be decided on a case to case basis. ETA aspirates are adequate for RT PCR diagnosis of COVID
- l. Liberation from MV: Standard weaning protocols with bridging to NIV with well fitted mask and dual limb circuits and strict airborne precaut

SpO<sub>2</sub><90% WITH OXYGEN>40%  
RESPIRATORY RATE>30  
HEMODYNAMIC INSTABILITY

ASSESS WORK OF BREATHING

Clinical detection of Excessive inspiratory effort  
Large swings in CVP, intercostal indrawing  
Oesophageal Pressure >-15cms H<sub>2</sub>O  
If on NIV: Generating large Tidal volume>9-9.5ml/Kg

HIGH

LOW

INVASIVE VENTILATION

FAIL<sup>1</sup>

NON-INVASIVE VENTILATION: HFNC/NIV<sup>#</sup>

Close Monitoring, Reassess 1-2 hours of initiation

LUNG PROTECTIVE VENTILATION  
P Plateau<30, Driving Pressure\* <15  
CONSERVATIVE FLUID STRATEGY

SpO<sub>2</sub><90  
FiO<sub>2</sub>>0.7  
NMB  
↓PEEP<sup>@</sup>

<sup>#</sup>ICU Ventilator  
Dual limb Circuits  
HMEF at Y connector  
Oronasal/Helmet interface  
Tight fitting mask (Non vented)  
BVF at Expiratory limb before machine

COMPLIANCE

COMPLIANCE >

<sup>1</sup> NIV FAILURE  
Respiratory Rate >28  
SpO<sub>2</sub><92%  
Escalating FiO<sub>2</sub>/PEEP  
P/F <150  
Mental Obtundation  
Hemodynamic instability

PHENOTYPE H  
TIDAL VOLUME:4-8ml/kg pbw  
Early Prone Ventilation, APRV  
Lung Recruitment manoeuvres  
Higher FiO<sub>2</sub> Lower PEEP Table

PHENOTYPE L  
TIDAL VOLUME:6-8ml/kg pbw  
(8-9ml/kg pbw if CO<sub>2</sub> remains high)  
Higher PEEP may be detrimental

Hypoxemia refractory to Prone ventilation or APRV>6hrs: Consider ECMO

ASSOCIATED CONDITIONS& MANGEMENT

Pulmonary Intra Vascular Coagulation  
(Increased D-dimer, Fibrinogen,  
Thrombocytopenia): HEPARIN/LMWH

CYTOKINE RELEASE SYNDROME  
Increased CRP, Ferritin, IL6  
Rx: STEROIDS/TOCILIZUMAB

SEPSIS/SEPTIC SHOCK: SSC GUIDELINES

Targets on MV  
SpO<sub>2</sub> 90-94%  
PaO<sub>2</sub>>55mmHg  
PaCO<sub>2</sub><40mmHg  
pH>7.3  
Pplat<30cmH<sub>2</sub>O  
DP<15

PHENOTYPE L  
Low elastance (Compliant lung)  
Low V/Q  
Low PEEP  
Low Lung weight  
Low recruitability

DP=Pplat-PEEP  
<sup>#</sup> Avoid BiPAP Machine  
<sup>@</sup> increase in increments of 2

High PEEP  
High Lung weight  
High recruitability

## 2. ECMO: Early evaluation & implementation

- i. ECMO Indications: Under optimal conditions (FiO<sub>2</sub>>0.8, Tidal volume 6ml/kg PBW, PEEP>10 and no contraindication for prone ventilation) and prone ventilation has been implemented and meet one of the following
    - a. PaO<sub>2</sub>/FiO<sub>2</sub><50 for more than 3 hours
    - b. PaO<sub>2</sub>/FiO<sub>2</sub><80 for more than 6 hours
    - c. PaO<sub>2</sub>/FiO<sub>2</sub><100 with FiO<sub>2</sub>=1
    - d. Arterial pH<7.25 and PaCO<sub>2</sub>>60 mmHg for>6hours
    - e. Arterial pH<7.20 and Plateau pressure >30cms H<sub>2</sub>O when Respiratory rate >35/minute
    - f. Concomitant cardiogenic shock or cardiac arrest
  - ii. ECMO contraindication:
    - a. Unrecoverable primary disease
    - b. Anticoagulation contraindicated
    - c. Mechanical ventilation > 7 days with higher settings (FiO<sub>2</sub>>0.9, Plateau pressure>30cm H<sub>2</sub>O), age older than 70 years, immunosuppression, presence of large peripheral vascular anatomy or disease
3. Choice of ECMO treatment: VV-ECMO. When circulatory failure of cardiac aetiology VA ECMO to be considered.

**d. Drainage of airway secretions:** Humidification with Heated humidifier /HME.CLOSED SUCTION device for Endotracheal suctioning.

**e. Hemodynamic & Volume status: CONSERVATIVE FLUID STATERGY**

- i. Close monitoring of cardiac function: Echocardiography, Troponin T/I, NT BNP, Right heart function with ECHO.
- ii. Tissue perfusion: monitoring and maintenance.
- iii. Causes of shock in COVID sepsis include:
  - Hypovolemia: Dehydration, Sepsis, Cytokine storm
  - Vasoplegia
  - RV failure: Due to ARDS, High ventilating pressure, Massive Pulmonary embolism (Assess by high CVP and with ECHO)
  - COVID myocarditis: Assess with ECG, biomarkers, Echocardiography

Find cause of hemodynamic instability (Systolic BP<90mmHg or 40 mmHg less than baseline, MAP<65mmHg, need for vasoactive drugs, severe arrhythmias) and treat the cause.

Arrhythmias should be actively managed.

Monitor clinically (Mental status, Urine output, capillary refill time, blood pressure, heart rate etc), functional hemodynamic monitoring like Passive leg raising test, Pulse pressure

variation, End expiratory occlusion, mini fluid challenge, Tidal volume challenge, IVC distensibility index, Echocardiography can be used in centres with such capability.

- iv. Volume status: Do not overload the patient with adequate tissue perfusion. Small boluses of fluid are given and close monitoring of response noted. If signs of overload further fluids to be restricted. Over load can be assessed by worsening PaO<sub>2</sub>/FiO<sub>2</sub>, Extra vascular lung water if resources permit.
  
- f.** Nutrition: Early enteral feeds preferred (if no contraindications like dysfunctional gut, severe hemodynamic instability) with high calorie and proteins. 25-30 Kcal/kg/day. Protein: 1.5-2 gm/kg. Supplemental/Total parenteral if not tolerating/ dysfunctional gut.
- g.** STEROIDS: As mentioned in medical management of COVID patient.
- h.** Antimicrobial: Routine use of antimicrobial is not recommended without clear evidence of bacterial infection.
- i.** Anticoagulant therapy: Mentioned in Medical management. UFH if abnormal RFT. Monitor coagulation profile & RFT
- j.** Sedation, Analgesia: Patient on Mechanical ventilation should be given appropriate sedation and analgesics. Options include propofol, fentanyl, midazolam.
- k.** MUSCLE RELAXANTS: Routine use not recommended. If dyssynchrony can use Cis atracurium or atracurium.
- l.** Acute Kidney Injury & Renal replacement therapy: Second stage KDIGO criteria (Creatinine=2-2.9 times baseline value, urine output <0.5 ml/kg/hr for 12 hours) and other evidence for the need of renal replacement therapy (RRT).
- m.** Infection transmission prevention:
  - i. Use of PPE as needed.
  - ii. HEPA BACTERIAL VIRAL filter placed at expiratory limb of ventilator tubing
  - iii. N95 mask / 3 ply mask for patient when on Nasal Cannula for Oxygen supplementation.
  - iv. All intensive care personnel (medical, nursing, allied health, cleaning and ward assistants) receive training in infection control and personal protection equipment.
  - v. Recommend minimising aerosol generating procedures. If they must be performed, then they should be completed in a negative pressure room. If this is not available, then a single room should be used.
  - vi. When a unit is caring for a confirmed or suspected COVID-19 patient, ensure that all donning and doffing are supervised by an additional appropriately trained staff member (buddy).

- vii. Recommend against the use of nebulised agents (e.g. salbutamol, saline) for the treatment of non-intubated COVID-19 patients due to the risk of aerosolization and transmission of infection to health care workers in the immediate vicinity.
- viii. Clamp the ETT while intubating and when disconnection is required like during changing to transport ventilator.
- ix. Allow time for complete muscle paralysis prior to intubation to avoid spontaneous exhalation by patient.

**Aerosol generating procedures include:**

- Intubation
- Extubation
- Bronchoscopy
- High flow nasal oxygen use
- Non-invasive ventilation (particularly with a poorly fitting mask)
- Procedures on screaming children
- Tracheostomy
- CPR prior to intubation

**5. Transfer out of ICU:**

Stable vitals, Oxygenation has improved (needs only Room air or low flow oxygen), weaned off from ventilator, Conscious, Respiratory rate<30/min, SpO<sub>2</sub>>93%, Stable hemodynamic, Not on support, No acute organ dysfunction.

**IV. INTUBATION: Process & Precautions:**

1. Ideally done in Negative Pressure room. If facility is not available intubate in single room/ward after taking all airborne infection control precautions. Treatment algorithms and cognitive aids needed should be displayed in the room.
2. Airborne precautions: For all staff in attendance: Fit check N95 mask, Goggles or face shield, Impervious gown, Gloves
3. Limit number of persons present at intubation site to 3, intubator, assistant and nurse.
4. Plans for difficult airway discussed beforehand.
5. Procedure to be done by the most qualified staff with the minimum number of health care personnel present as are required to undertake a safe intubation.
6. Video laryngoscopes should be used preferentially
7. Mac Coy Blades / intubating stylets use to minimise duration and easiness of intubation.
8. Oral Intubation preferred.
9. Preoxygenate-**Spontaneous** breathing with high FiO<sub>2</sub> to minimise Bag mask ventilation
10. Use of viral filter on bag mask Circuit
11. Clamp endotracheal tube while intubating.

12. Post intubation positive pressure ventilation started only after inflating the ETT cuff and confirming position of ETT (ideally with EtCO<sub>2</sub>)
13. Endotracheal tubes with sub glottic suction aid preferred
14. Closed suction device to be used to prevent disconnections of circuit for removal of secretions
15. All intubation equipment including those for Difficult airway should be near the patient to prevent multiple exits & entry of health care personal.

#### **V. TRANSPORT OF PATIENT:**

1. Movement of patients with COVID-19 should be limited with all efforts made to ensure the patient is initially admitted to the appropriate location.
2. Non-intubated patients should be transferred wearing a surgical mask over their oxygen delivery device.
3. All staff must wear airborne PPE.
4. Once a patient is admitted to the ICU, transport outside of the ICU should be limited. If transport is required, then coordination at a senior level is mandatory to ensure safety standards are maintained
5. Hallways must be cleared where possible and only essential staff should accompany the patient. Staff not involved in the transfer should not come within 2 metres of the patient.
6. Intubated patients should have closed circuits with a viral filter in situ.

#### **VI. PEEP:** Optimal PEEP -one that has adequate oxygenation without affecting oxygen delivery to tissues. (Does not affect hemodynamics)

- Step wise increment of PEEP at 2 increments monitoring hemodynamics.
- Static compliance method
  1. Volume controlled Ventilation
  2. Set pressure limit 10-15 cm H<sub>2</sub>O above ventilating pressure (or per institutional policy).
  3. Turn ventilator sighs off for the procedure if being used.
  4. Explain the procedure to the patient and to be as relaxed as possible.
  5. Sedation/ relaxants sos
  6. All measurements be obtained under the same conditions
  7. Upright as possible.
  8. Determine the static compliance at 0 cm PEEP.
  9. The tidal volume, peak and plateau pressures should be noted.
  10.  $V_t/P_{plat}-PEEP = \text{Static compliance}$
  11. Determine Static compliance at 3,6,9,12,15 cms H<sub>2</sub>O of PEEP
  12. The patient should be placed on the lowest PEEP level providing the greatest static compliance



## **VII. Recruitment: On a case-to-case basis. Methods:**

1. 40cmH<sub>2</sub>O for 40-60 seconds
2. 3 consecutive sighs/min with a plateau pressure of 45cmH<sub>2</sub>O
3. 2 minutes of peak pressure of 50cmH<sub>2</sub>O and PEEP above upper inflection point (obese/trauma patients may require >60-70cmH<sub>2</sub>O)
4. long slow increase in inspiratory pressure up to 40 cmH<sub>2</sub>O (RAMP)
5. stepped increase in pressure (Staircase Recruitment Maneuver)

## **VIII. General care of Critically ill patients in ICU:**

1. VAP prevention
2. Spontaneous Awakening & breathing Trials
3. Change in position 2Hourly
4. DVT Prophylaxis
5. Stress related mucosal disease prophylaxis
6. Nutrition
7. Psychological support
8. Debriefing

## **IX. Cardiac Arrest: AHA 2020 with modification to limit transmission**

Recognize cardiac arrest. Look for absence of signs of life and normal breathing and feel for carotids. Do not listen or feel for breathing by putting your ear or cheek close to patient's mouth.

- ❖ Avoid mouth to mouth or pocket mask ventilation
- ❖ The staff **should have** gown, gloves, eye shield or goggles before starting CPR (complete aerosol generating procedure PPE).
- ❖ Start CPR with chest compression.
- ❖ If patient is having oxygen mask before start of CPR leave it in situ to limit spread of aerosol. Otherwise if readily available put a mask and start CPR. Limit entry of people into the room during CPR.
- ❖ For bag and mask ventilation, connect HME or **bacterial filter** to it to limit aerosol generation. Use 2-person technique for bagging, one person to hold the face mask tight with E-V technique while the other ventilates to minimise aerosol generation.
- ❖ Identify and treat any reversible causes.
- ❖ Defibrillate shockable rhythms rapidly

Reference

1. WHO: Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected Interim guidance 13 March 2020
2. The Australian and New Zealand Intensive Care Society (ANZICS) COVID-19 Guidelines Version 1
3. Government of India Ministry of Health & Family Welfare Directorate General of Health Services (EMR Division) Guidelines on Clinical Management of COVID – 19
4. WHO: Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected Interim guidance 25 January 2020
5. Resuscitation council UK. Resuscitation of COVID – 19 patients in hospital. March 2020. (reference for cardiac arrest recommendations)
6. COVID-19 pneumonia: different respiratory treatment for different phenotypes? L. Gattinoni , D. Chiumello , P. Caironi , M. Busana , F. Romitti1 , L. Brazzi4 , L. Camporota
7. Gattinoni et al, 2020 – Covid-19 Does Not Lead to a “Typical” ARDS -INTENSIVE Review Aidan Burrell

FiO<sub>2</sub>-PEEP TABLE

**Lower PEEP/higher FiO<sub>2</sub>**

<b>FiO<sub>2</sub></b>	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
<b>PEEP</b>	5	5	8	8	10	10	10	12

<b>FiO<sub>2</sub></b>	0.7	0.8	0.9	0.9	0.9	1.0
<b>PEEP</b>	14	14	14	16	18	18-24

## 11. Treatment in pregnancy

### 1] Categorization of COVID 19 in pregnancy

Though the ICMR guidelines consider pregnancy as a potentially immune-compromised state and hence put all pregnant women into category B, it may be well worthwhile to formulate a separate set of categories that would be specific to pregnancy which would also allow better patient treatment plans.

A thorough history, especially with regard to covid symptomatology, extensive review of records, and a well done general and Obstetric examination is a must before categorizing women into B1, B2 and C.

#### Categorization of Pregnant Women with COVID 19 infection

B1	The asymptomatic pregnant woman
B2	The pregnant woman with ILI symptoms( fever, cough, rhinitis, sore throat) or diarrhoea or fatigue , or those with co morbidities like hypertension, diabetes, liver disease, renal disease
C	The pregnant woman with either breathlessness, chest pain, drowsiness, or hypotension, hemoptysis , cyanosis [red flag signs]

\*Categorization should be reassessed every 24 hours for Category B1 & B2 based on symptoms and walk test.

\*Severe fatigue and malaise and persistent fever, though not classically red flag signs, usually indicate active disease and it is in these cases that the pro inflammatory markers need to be looked at closely. One can expect deterioration in this subset.

Also, it may be well to understand that the fever in COVID 19 can be prolonged and unrelenting.

### 2] Clinical stages of severity

Mild	no breathlessness or hypoxia, RR < 24/mt, spO2 > 94% on room air, and otherwise asymptomatic
Moderate	Dyspnea and / or hypoxia , RR 24-29 / mt, spO2 91-94% on room air, or fever and cough
Severe	Dyspnea and / or hypoxia RR> 30 breaths/ mt or spO2 < 90% on room air or a pulse rate > 125/mt with or without pneumonia

### 3] When to admit and where and how to manage?

#### 3.1. Category B1:

- The lady can be allowed care at home provided they are able to self-isolate and are < 34 weeks of pregnancy. They must preferably procure a pulse oximeter for personal use.
- Dietary advice and avoidance of total bed rest must be emphasized.
- Iron calcium folic acid are to be continued.
- They must report to the nearest facility if they become symptomatic or if they have a fall in spO<sub>2</sub> < 94%
- Also they must be taught to do the walk test – whereby they walk for 6 mts or take 40 steps and are told to measure their spO<sub>2</sub> before and after – a fall of > 3 % from baseline is significant and they must report to the health facility.
- Women with gestational age more than 34 weeks is admitted in CSLTC for proper work up and observation. If stable, she may be discharged to continue care from home with instructions to report if any symptoms of the disease or pain or leaking or bleeding or diminished fetal movements. She is not discharged if close to term.

#### 3.2 Category B2:

- She may be cared for in a CSLTC as they will need symptomatic treatment and laboratory investigations. Daily check on vitals including RR and spO<sub>2</sub> is a must. Walk test will allow professionals to pick up problems earlier.
- Symptomatic treatment may include paracetamol, anti-tussive, and oseltamivir 75 mg bd x 5 days in addition to the routine iron, calcium and folic acid.
- Lab investigations to be sent are CBC, RFT, LFT, RBS, S.electrolytes, ECG, CRP.
- It may be advisable to ask for an Xray chest PA view with lead shielding of the abdomen in all cases who have a persistent cough. Additional markers like d - dimer, ferritin, CPK are to be sent are persistent . MDI/DPI Budesonide 800mcg twice a day can be started if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset. They should be monitored by thrice daily recording of temperature, pulse rate, respiratory rate, SPo<sub>2</sub> and Walk test and review of symptoms.
- Once patients have been worked up and are stable with subsidence of symptoms, they can go into home quarantine with the same checks as detailed for others on quarantine.

#### 3.3 Category C:

- These patients require multi-disciplinary care and must therefore be admitted in Covid designated hospitals.
- A thorough history, especially with regard to covid symptomatology, extensive review of records, and a well done general and Obstetric examination is a must.

##### 3.3.1 Laboratory investigation for admitted COVID 19 positive patients

At Admission CBC, RFT, LFT, CRP, RBS, S. electrolytes,

ECG, Pulse oximetry.

If clinically Indicated Portable CXR, D-Dimer, Ferritin, LDH, CPK, procalcitonin, Blood culture, TROP T/I, HRCT Thorax [only in case of worsening]

To repeat Every 48 hours if clinically deteriorating.

CBC, Creatinine, AST/ALT, CRP, LDH, CPK, Ferritin, D Dimer.

For Immunocompromised patients eg Transplant recipients, HIV

Tests to rule out opportunistic infections like Mycobacterium tuberculosis, pneumocystis jiroveci etc

**To note:**

- Pulse rate: If < 100/mt it is reassuring. If between 100-110 b/mt she needs closer observation.
- If > 110/mt ECG to be looked into closely and she is categorized a high risk if it crosses 125/mt.
- RR and spO2 need careful monitoring.

RR spO2

Mild <24 breaths/mt >94% on room air

Moderate 24-29 breaths/mt 91-94% on room air

Severe 30 and> breaths/ mt <90% on room air

**3.3.2 Values to remember for the pro inflammatory markers:**

Marker Normal value High risk

CRP < 5 CRP > 100 mg /L

D Dimer 1st trimester: 169-1202mcg/l

2nd trimester: 393- 3258 mcg/l

3rd trimester: 551- 3333 mcg/l

Ferritin < 60 Ferritin > 300mcg/L

LDH < 400 LDH > 400 U /L

#NLR >3.13, \*ALC < 0.8

\*ALC – Absolute lymphocyte count #NLR – Neutrophil lymphocyte ratio [NLR – should be calculated prior to steroid administration

• Xray: chest- PA view with abdominal shielding to be taken if there is a persistent cough or dyspnea

• Look for lower lobe consolidation, fluffy opacities.

• HR CT Thorax – if there is worsening of signs, symptoms even after steroids and oxygen.

### 3.3.3. Steroid trigger

MDI/DPI Budesonide 800mcg twice a day started when the symptoms (fever and/or cough) are persistent beyond 5 days of disease onset.

Parenteral/oral steroids can be started when

1. Moderate to severe rise in RR or a fall in spO<sub>2</sub> even without pneumonia
2. 3% desaturation with 6-minute walk test
3. Bronchopneumonia and
4. Marked rise in pro inflammatory markers with symptoms.

For the last two indications, steroids are started as per opinion of internist/pulmonologist.

Start with Inj Dexamethasone 6 mg 12th hourly for 4 doses, followed by Intravenous Methyl prednisolone 0.5-1 mg/kg or 40 mg OD or oral Prednisolone 40 mg OD for 10 days or until discharge whichever is earlier. Higher dose of steroids may be needed in severe cases and can be decided by multi-disciplinary team. If lung maturity is not an issue, Inj Dexamethasone may be skipped.

Monitor sugars while the patient is on steroids and expect a marginal increase in TC. Correlate with ALC and NLR. Methyl Prednisolone does not cross the placenta and hence cannot be a substitute for the dexamethasone that is used to enhance lung maturity.

### 3.3.4. LMW heparin trigger:

- All admitted patients in category B2 and C in third trimester are to receive prophylactic Enoxaparin at:
  - 40 mg sc od if between 50-90 kg
  - 60 mg sc od if between 90-130 kg
- LMWH has to be stopped 12 hours prior to delivery/ C section (24 hours if taking higher doses)
- Higher dose of enoxaparin may be needed in category C hypoxic severely ill patients and those with very high d dimer values. If the d dimer is very high or there are progressively increasing values, due consideration is to be given to stepping up the dose to 60 mg bd provided there is no enhanced risk of bleed.
- The same may be continued for 10 days in the post-partum. Thrombocytopenia may be associated with severe Covid 19 infection. For women with platelet count less than 50,000/mm<sup>3</sup>, LMWH and aspirin has to be discontinued. Since women tend to be discharged early, and if they can't take the injections at home, low dose aspirin at 150 mg/day HS can be considered a viable option for 2-3 weeks.
- VTE scoring must be done and duration of thromboprophylaxis to be modified accordingly. Hydration and ambulation are to be ensured.
- If women are admitted with confirmed COVID 19 infection within 6 weeks post-partum, thromboprophylaxis should be offered for the duration of hospitalization and continued at least

10 days after discharge. For those with significant comorbidity, duration of thromboprophylaxis may be extended to 6 weeks post-partum

#### 3.3.5. Antibiotic policy:

- If there is evidence of bacterial superinfection consider antibiotics as per institutional antibiotic policy

#### 3.3.6. Remdisivir:

- May be indicated in Category C with bronchopneumonia not responding to steroids and oxygen.
- Its safety in pregnancy though not yet established, it may be offered on a compassionate basis with written informed consent.
- It needs to be started within 10 days of onset of symptoms.
- Recommended dose is 200mg IV on day1 , followed by 100 mg daily iv x 4 days
- RFT and LFT must be normal and it is preferable to do a creatinine clearance.
- Ivermectin and Favipiravir are contraindicated in pregnancy.

#### 3.3.7 Tocilizumab

- Use in pregnant patients must be made on a case-by case-basis to be decided by the multidisciplinary team on compassionate ground with informed consent.

#### 4] When to Deliver?

- Decision for delivery is to be taken purely on obstetric grounds.
- Sometimes the decision is to be made for resuscitative purposes. It is to be taken by multidisciplinary team and is to be considered beyond 26-28 weeks on individual basis, if patient deteriorating and not responding to NIV and if invasive ventilation is needed.
- The mode of delivery depends on emergent nature and will be more often by Cesarean section. The decision will also be dictated by general condition of the patient and her ability to deliver.

#### 5] Intrapartum care:

- Labour should be conducted in dedicated covid labour room. Category B1 and low risk B2 women in labour need not be monitored by CTG but may be used for ease of monitoring as auscultation in PPE is technically difficult.
- In addition to routine parameters monitored in labour, SPO2 also has to be closely monitored.
- Decision for caesarean section can be taken earlier than usual, considering the time delay in shifting and getting the COVID operation theatre and staff ready.

#### 6] Post-Partum Care:

- Breast feeding can be permitted. Mother must wear masks and wash hands before and after feeding the baby. Encourage oral hydration, ambulation of patient.
- All post LSCS patients in covid ward should be given LMWH 40 mg od x 10 days.

- Patients should be taught to take LMWH by self after discharge.
- Antibiotic prophylaxis guideline is to follow institution protocol.

## 7] Discharge guidelines:

### Category B:

- Rapid antigen Test( RAT) negativity is not essential prior to discharge for category B1 and B2.
- The patient may be sent home / to CSLTC if there are no symptoms for 72 hrs and the lab results are normal. They should be off anti pyretics, no oxygen and should not be fatigued.
- Once discharged a total of 17 days of isolation is recommended from onset of symptoms or from diagnosis.
- While in quarantine, the patient must follow the same set of instructions as in 3.1. They must preferably procure a pulse-oximeter for personal use.
- Dietary advise and avoidance of total bed rest must be emphasized. Iron calcium folic acid are to be continued.
- Thromboprophylaxis with LMW heparin for a total of 10 days. Low dose aspirin at 150 mg/day HS for 2-3 weeks can be considered in low risk women especially if they can't take injections at home. They must report to the nearest facility if they become symptomatic or if they have a fall in spO2 < 94%.

### Category C:

- RAT to be done on day 14 from onset of symptoms.
- If negative and no symptoms for 3 days, afebrile , not requiring oxygen , the patient may be discharged.
- Follow up in any hospital of her choice or in a post covid clinic in 2 months post-natal.
- If patient is still not well even after being RAT negative, she may continued to be cared for in a covid ward/ ICU or in the non covid side.
- If RAT is still positive even after 14 days, repeat every 48 hrs until negative

## 8] Follow up of Covid 19 affected pregnancies

- After recovery, the lady can be followed up in any hospital of her choice if undelivered.
- Standard antenatal care is provided. The need for a detailed anomaly scan is to be emphasized for a woman affected by Covid in first trimester.
- Undelivered women in late second and third trimester of pregnancy need to get an ultrasound done after 2 weeks to assess fetal growth.

## References

- Covid 19 treatment guidelines for pregnancy-FOGSI-Kerala
- Coronavirus (COVID-19) infection in pregnancy, RCOG, 19th Feb 2021



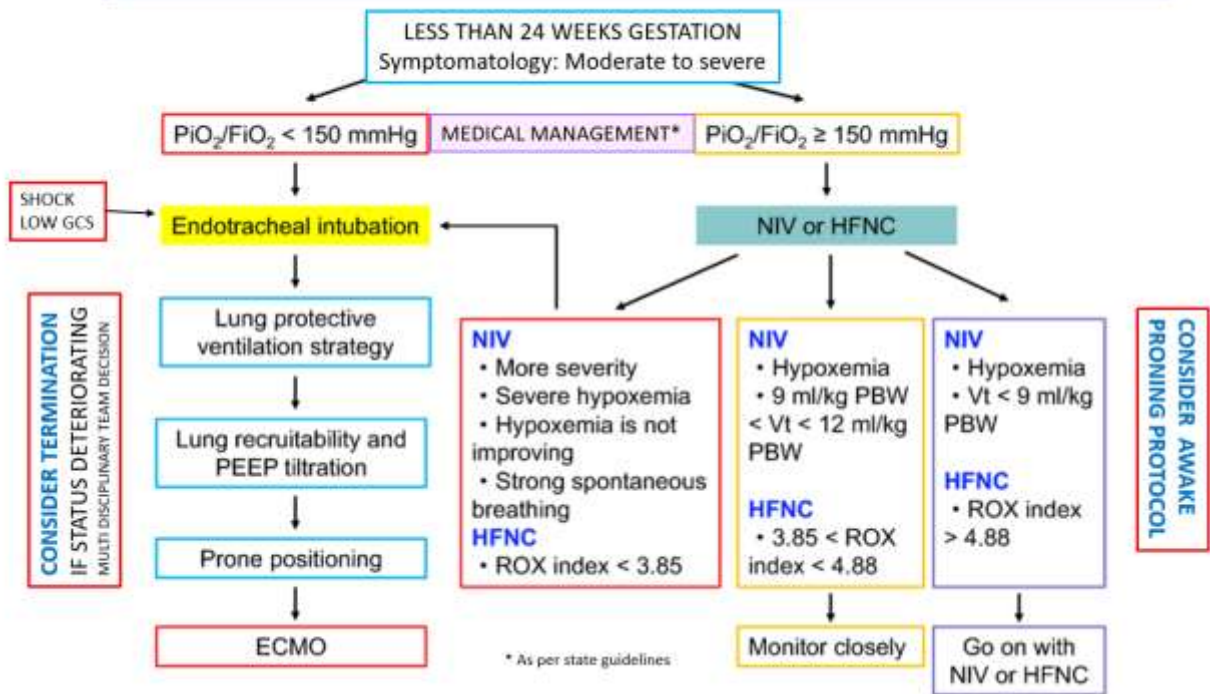
## COVID 19 CRITICALLY ILL PREGNANT PATIENTS

1. Major changes during pregnancy that can put additional burden on COVID + mother
  - a. Increased cardiac output
  - b. Dilutional anaemia
  - c. Sinus tachycardia
  - d. Decreased Systemic vascular resistance
  - e. Decreased colloid osmotic pressure
  - f. Decreased colloid osmotic pr.-pulmonary capillary occlusion pressure gradient
  - g. Procoagulant state-increased Venous thrombo-embolism
  - h. Increased oxygen consumption
  - i. Increase in Minute volume
  - j. Decreased Functional residual capacity
  - k. Associated gestational diseases and its complications
  
2. CONTINUING PREGNANCY:
  - a. Stress on compromised cardio-respiratory system
  - b. Hypoxemia –impaired foetal oxygenation
  - c. Prothrombotic and hyperinflammatory state
  - d. Higher Oxygenation goals
  - e. Drugs: Compassionate /EUA use
  - f. Progress not predictable
  - g. Slow reversal of COVID pneumonia
  - h. Prone position difficult
  - i. CXR CT technically difficult
  
3. Less than 24 weeks Asymptomatic / Mild severity:
  - a. Home care with monitoring chart, review and hospital admission as indicated
  - b. Awake repositioning (as tolerated)
  - c. Investigations:  
BRE, LDH, CRP, D dimer
    - i. Base line: @ diagnosis
    - ii. 5<sup>th</sup> day of symptoms
    - iii. 8<sup>th</sup> day of symptoms
    - iv. 11<sup>th</sup> day of symptoms

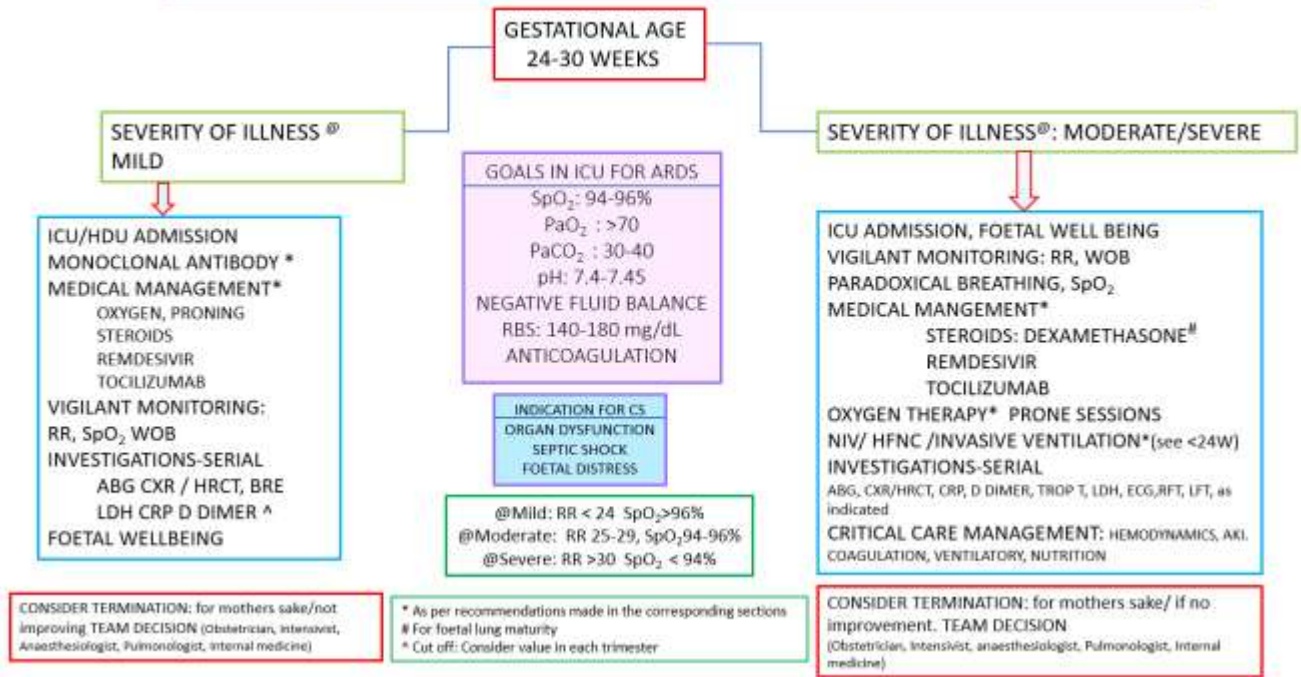
	8 am	2 pm	8pm
Heart rate			
Respiratory rate			
SpO <sub>2</sub>			
WOB*/Distress			
Severe cough			
Fatiguability			
6 min/40 step (as tolerated) walk test- SpO <sub>2</sub> fall			
Temperature			
Urine output			
Mentation			
Bleeding PV			

\*WOB: Work of breathing

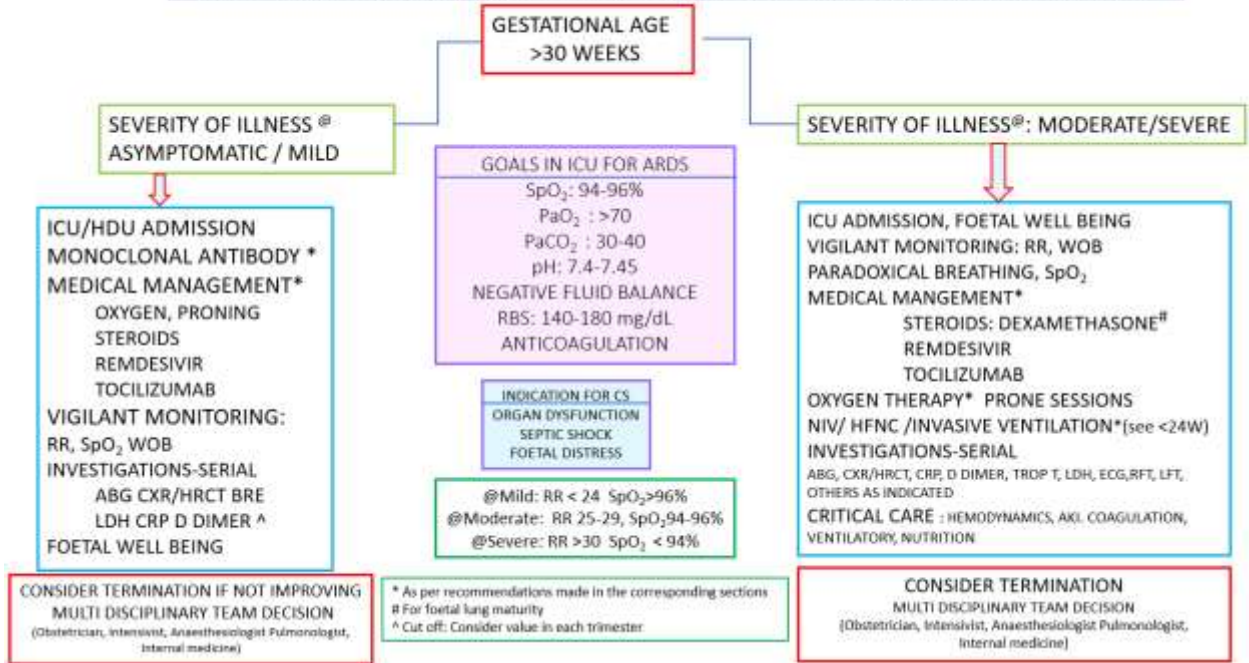
STRUCTURED ASSESSMENT, CONTINUOUS MONITORING, TIMELY INTERVENTION



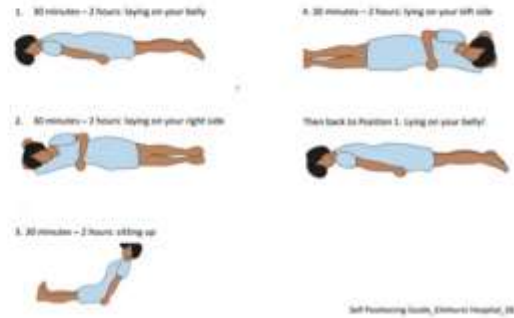
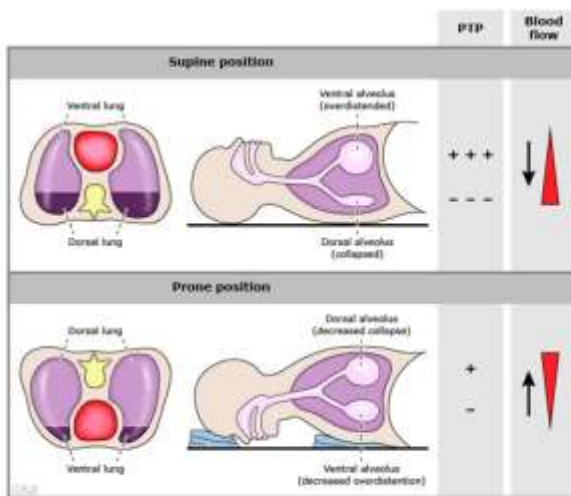
STRUCTURED ASSESSMENT, CONTINUOUS MONITORING, TIMELY INTERVENTION



STRUCTURED ASSESSMENT, CONTINUOUS MONITORING, TIMELY INTERVENTION



# AWAKE REPOSITIONING PROTOCOL



## 4. MEDICAL MANAGEMENT:

- MONOCLONAL ANTIBODY:** As per guidelines under section Monoclonal antibody
- STEROIDS:** As Oxygen therapy initiated
- Methylprednisolone
- Dexamethasone/ Betamethasone for foetal lung maturity
- REMDESIVIR: See section: Remdesivir
- TOCILIZUMAB: Acute clinical worsening. EUA/Compassionate use

## **12. GUIDELINES ON CLINICAL MANAGEMENT OF COVID 19 INFECTION IN CHILDREN**

Coronavirus disease 2019 (COVID-19) caused by SARS COV 2 (severe acute respiratory syndrome coronavirus 2) is rarer in children compared to adults. Incidence of disease in children has been reported to be around 2% in most studies. Exact cause of lower incidence is not known. It may be due to age related differences in expression, affinity and distribution of ACE receptors, less comorbidities like Obesity and Diabetes Mellitus or less age-related damage to endothelium. Nevertheless, severe manifestations and deaths are being increasingly reported in children and they can act as an important source of infection for adults and health care workers as they cannot follow cough etiquettes as efficiently as adults.

### **Clinical Features**

Incubation period ranges from 2 - 14 days, with a median time of 4-5 days. Asymptomatic and presymptomatic infection has also been reported. Clinical syndromes associated with COVID infection include mild uncomplicated illness with fever, sore throat, malaise, cough, diarrhoea or vomiting, mild pneumonia, severe pneumonia, ARDS, sepsis and septic shock with multi organ involvement. Covid illness most often starts with mild symptoms like dry cough and sore throat. 10% of patients may present with GI symptoms like diarrhoea and vomiting, while rhinorrhea is relatively rare (7.5%). Anosmia, ageusia and GI symptoms may precede development of respiratory symptoms. Patients may also complain of myalgia, headache, and fatigue. Fever and cough are seen less frequently in children than adults. Elderly and immunocompromised may present with atypical symptoms like fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium, and absence of fever. Leucopenia is uncommon in children compared to adults. At admission 30% of symptomatic children may have leucopenia and 10 - 20% may have elevated CRP. Leucopenia and CRP > 10mg/dl has been found to be associated with pneumonia (12).

### **Clinical progression and complications**

Clinical course may be hyper acute with rapid onset of fever and breathlessness or moderate with slower progression of symptoms and later recovery or biphasic with late progressive worsening and multi organ involvement. Illness severity can range from mild to critical.

**Multisystem inflammatory syndrome in children (MIS-C)** may occur 4 to 6 weeks after a patient is infected with Covid-19(4). MIS – C should be considered in any child presenting with fever with high inflammatory markers ( high CRP, ESR, Ferritin, Fibrinogen, D Dimer, LDH, IL- 6, elevated Neutrophils, low lymphocytes, Low albumin etc) with multi system (>2) organ involvement causing severe disease requiring admission, with no plausible alternative diagnosis and evidence of recent or past Covid infection as evidenced by positive RT PCR, antibody or

antigen study or exposure to a suspected or confirmed Covid 19 case within the 4 weeks prior to admission. Multisystem inflammatory syndrome is being reported in adults also

### **Risk factor for severe disease**

Age is an important risk factor. Case fatality rate is more in elderly, infants less than 1 year and in those with comorbidities like malignancy, chronic lung, liver, kidney, neurological disease and in those with congenital or acquired immunodeficiency. Case fatality rate in children is less than 1%. Lymphopenia, neutrophilia, elevated SGOT, SGPT, LDH, CRP, Ferritin and D dimer is associated with more severe illness.

### **Reinfection and persistent RT PCR positivity**

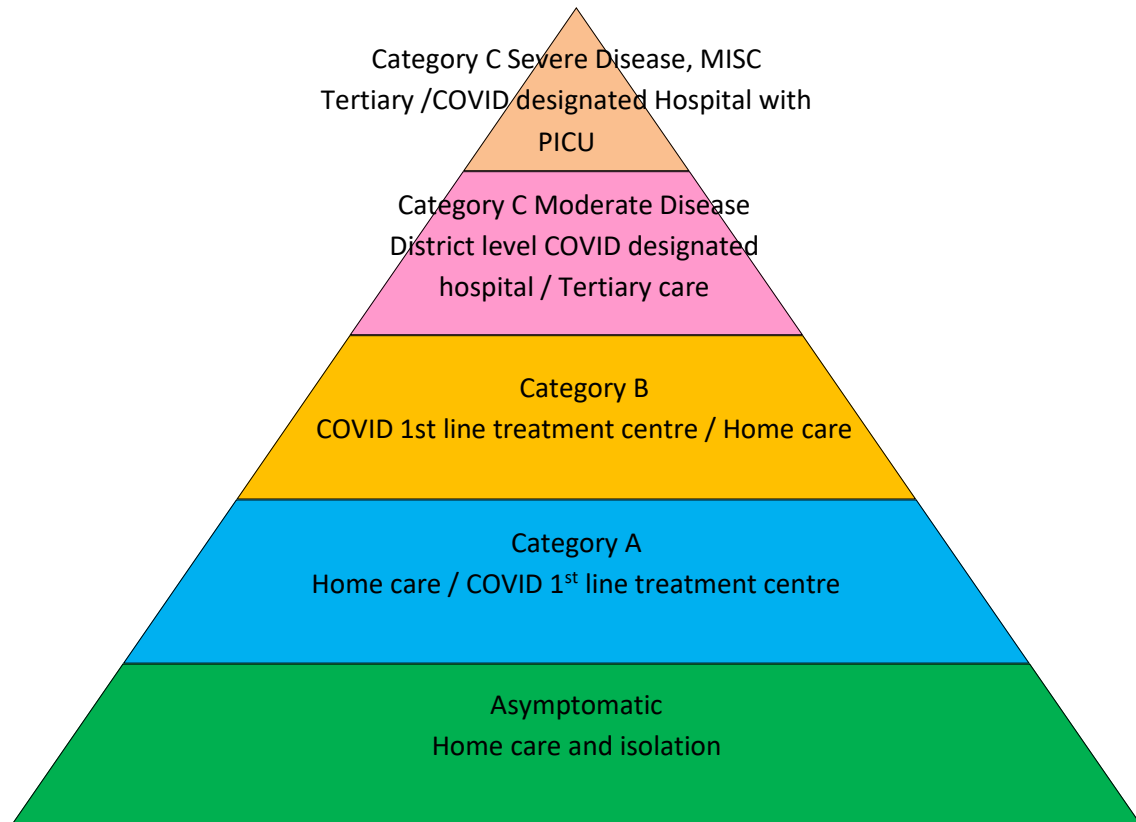
Viral RNA shedding decreases with resolution of symptoms but may continue for days to weeks. Median range of viral shedding in hospitalized patient is 12 – 20 days. Presence of RNA during convalescence does not necessarily indicate viable infectious virus. Detection of IgM and IgG antibody often correlates with clinical recovery and immunity. Reinfections though very rare are being reported.

### **Triage Policy for children with COVID 19 Infection**

- Category A patients: Children tested positive but asymptomatic or mildly symptomatic with category A symptoms may be cared at home.
- If category A children have persistent fever or worsening cough of more than 5 days duration, they need to be referred to Taluk hospitals or hospitals with pediatric facility to look for causes of persistence of fever.
- If category A children develop any danger signs like inability to feed, increased somnolence, poor feeding, fast breathing, bluish discoloration, chest indrawing, altered sensorium or seizure they need to be referred to district level hospitals with HDU facility / tertiary care.
- Category B patients may be cared in CSLTC or at home if a reliable caretaker capable for caring and monitoring the child is available. These children should have access to primary physician or specialist through phone.
- Children with category C moderate disease should be cared in district level facilities with HDU care.
- Children with Category C severe disease should be cared in district level facilities / tertiary care with PICU facilities

\*HDU is a facility with provision for 24 hours monitoring, oxygen delivery through nasal prongs, mask, venturi or HFNC and monitoring with pulse oximeter.

\*\*PICU is a facility with central oxygen, invasive and non invasive ventilation, multichannel monitors, infusion pumps for accurate delivery of drugs etc The unit should be led by paediatrician or anaesthetist with paediatric critical care exposure.



<b>Table 1: Risk categorisation of patients with acute Covid 19 infection</b>		
Category A	Category B	Category C
Mild sore throat, cough, Rhinorrhea, Diarrhoea, Vomiting	Fever, severe sore throat, increasing cough.  Category A patients with comorbidities like Chronic heart, kidney, lung , neurological or liver diseases, obesity*, children on long term steroids, congenital or acquired immunosuppression.	Breathlessness, inability to feed, reduced activity / lethargy, altered sensorium, seizures , breathlessness, cyanosis, hypotension, Respiratory distress, spo2 < 94%,
<i>*Adolescents with obesity are at higher risk of having severe disease.</i>		

<b>Table 2: Clinical categorization based on severity of illness</b>		
Mild	Moderate	Severe
Category A & B	Category C	Category C
<b>Uncomplicated URI</b> fever, sore throat, rhinorrhea etc  <b>Without hypoxia or breathlessness.</b>	<b>Tachypnea (RR)*</b> < 2 months: $\geq 60/mt$ 2–11 months: $\geq 50/mt$ 1–5 years: $\geq 40/mt$ > 5 years: $>30/mt$  <b>Spo2 90- 94%</b>	<b>Spo2 &lt; 90%,</b>  <b>Danger signs</b> like inability to feed, grunting, lower chest in drawings, altered sensorium,lethargy, seizures, somnolence, hypotension, ARDS, MODS
*RR- Respiratory rate		



**Table 3: Treatment Of Acute Covid 19 Infection in Children**

Mild Disease	Moderate Disease	Severe Disease
Home care / CFLTC / CSLTC	Designated District Level Hospital / tertiary care center	Designated Covid hospital / tertiary care center with ICU facility
<p>Symptomatic treatment</p> <p>Paracetamol 10 -15 mg/kg/dose may repeat 6 hourly (Avoid other NSAIDS)</p> <p>ORS and Zn for Diarrhea</p>	<p>Paracetamol 10 -15 mg/kg/dose may repeat 6 hourly (Avoid other NSAIDS)</p> <p>Maintain fluid and electrolyte balance. Encourage Oral / NG feeds. If not tolerating IV fluids</p> <p>Salbutamol by MDI and face mask with spacer (only if wheeze present)</p> <p>ORS and Zn for Diarrhea</p> <p>Spo2&lt; 94% - Oxygen by prongs, venturi or face mask (Target Spo2 between 94 – 98%)</p> <p>Consider awake prone position in older children</p>	<p>Admit in ICU / HDU</p> <p>If spo2 &lt; 90% on nasal prongs with minimal work of breathing options include :</p> <p>Face mask at &gt; 5LPM flow (Fio2 40-60%)</p> <p>Oxygen hood at &gt; 5LPM flow (Fio2 30 - 90%)</p> <p>Venturi mask (28-60%Fio2)</p> <p>Non rebreathing mask at 10 -15LPM (Fio2 80-90%)</p> <p>High flow nasal cannula</p>
No antivirals or other drugs	<p>Amoxicillin in children &lt; 5 years or clinical suspicion of bacterial infection.</p> <p>Steroids if rapid progression and beyond 5 days from onset (any one):</p> <p>Methyl prednisolone 0.5mg/kg/dose BD or Dexamethasone 0.15mg per kg per day OD or</p>	<p>Empiric antibiotics</p> <p>Parenteral Steroids for 5 to 14 days</p> <p>Methyl prednisolone 1mg/kg/dose BD or Dexamethasone 0.15mg per kg per dose twice daily.</p> <p>+/- Inj. Remdesivir*</p>

		prednisolone 1mg/kg/day oral in patients with hypoxia	Restrictive fluid strategy Consider awake prone position in older children
No Investigations		If symptoms persist / hypoxia develops  CBC, Chest X ray, RFT, LFT, CRP, D Dimer, Ferritin (if available)	CBC, RFT, LFT, CRP, D Dimer, Ferritin  Chest imaging  Echo  Assess for Thrombosis / HLH / organ failure
Bring to hospital if any one present:		If any of these develops	If no response to HFNC in 1 hour/ increased work of breathing <sup>#</sup>
Fever lasting for more than 5 days / worsening cough  Look for alternate cause Send CBC, CRP, RUE	Poor feeding, fast breathing, bluish discoloration, chest indrawing, altered sensorium, seizure	Increased work of breathing Saturation less than 94% inspite of oxygen support Hemodynamic compromise Multi organ dysfunction Altered sensorium	Non invasive ventilation (if no response in 1 hour)  Invasive ventilation ((Low Tidal Volume, Optimal PEEP, Cuffed ET tube, Fluid restriction)  If no response - ECMO
Refer to Taluk Hospital with pediatric ward	Refer to District Hospital / tertiary care Hospital with HDU care after	Refer to tertiary care Hospital with PICU facility	Manage shock with isotonic crystalloid boluses (NS/ RL/PL) of 10 -20ml/kg over 30 - 60 minutes  Titrate inotropes if shock uncorrected

	stabilization		
<p>* Remdesivir has no mortality benefit hence no more recommended by WHO. It was found to decrease duration of hospital stay. Being an antiviral drug has role only early in disease. Dose 5mg/kg on day 1 (max.200mg) followed by 2.5mg/kg OD for 4 days. Avoid in those with renal or liver dysfunction. In special situation with guarded prognosis like patients with malignancy, those on immunosuppression etc. who present within 5 days of symptom onset with severe disease, use may be considered after medical board concurrence</p> <p>Surgical mask for older children &gt; 5 years and hood with side ports covered with surgical mask for children on oxygen support to decrease aerosolization and droplet spread.</p>			

Table 4: COVID 19 SYMPTOMS / SIGNS AND CLINICAL CATEGORISATION				
	ASYMPTOMATIC	MILD	MODERATE	SEVERE
Respiratory rate	Normal			
SpO2 in room air	≥94%	≥94%	90 – 94%	<90%
Grunting	No	No	No	+ /-
Severe chest retractions	No	No	No	+ /-
Lethargy/ somnolence	No	No	No	+ /-
Seizure	No	No	No	+ /-

Table 5: Template for recording signs and symptoms								
Time	Lethargy/ malaise	Breathlessness	Temperature	Pulse rate	Respiratory Rate	Chest indrawing	SpO2	BP

## **Treatment of severe and critical patients**

### **Monitoring**

Vital signs: including heart rate, RR and Spo2, Blood pressure  
Work of breathing: Watch out for increased work of breathing like retractions especially more than 2 site retractions, grunting, head bobbing, air hunger, large tidal volume breaths etc as these may indicate need for escalation of respiratory support inspite of having acceptable oxygen saturation.

Oxygen requirement: Monitor Oxygen requirement and provide appropriate oxygen delivery device. Target spo2 is  $\geq 94\%$  during resuscitation and 92 - 96% for those on oxygen therapy.

### **Laboratory investigations**

- Routine investigations: CBC with differential count and ESR, CRP. Unlike adult patients with COVID-19 there have been no consistent leukocyte abnormalities reported in paediatric patients
- Organ functions: RFT, LFT, Coagulation Profile, ECG daily. Chest X-ray may show patchy infiltrates consistent with viral pneumonia and chest CT scans may show nodular ground glass opacities and evidence of peripheral consolidation which may later progress to involve the whole lung fields.
- Risk markers: CRP, D Dimer, Ferritin, Troponin I. Send these every 48 hrs in patients with worsening respiratory status with severe or critical disease. Elevated D Dimer is an independent risk factor for mortality in adults.

### **Hyperinflammatory syndromes**

Some patients with Covid 19 infection may progress to multi organ failure due to hyperinflammatory syndromes like multi system inflammatory syndrome similar to Kawasaki disease, cytokine release syndrome or infection associated HLH often leading to multi-organ failure. Pointers towards hyper inflammatory syndromes include - Persistent high fever or reappearance of fever., rising CRP especially more than 100- 200 mg/L, doubling of ferritin in 24hours or very high ferritin levels ( $> 2000 - 10,000\text{mcg/L}$ ), falling counts, rising or falling ESR, increasing CPK, LDH and new onset shock especially with elevated Top i/ TropT.

### **Steroids**

Steroids may be considered in patients requiring oxygen support showing rapid worsening and in those with severe disease. Dose: Methyl Prednisolone 1- 2mg/kg/day for 5- 14 days. Or dexamethasone 0.15 mg/kg/dose OD or BD

### **Respiratory support in moderate cases**

If patient has hypoxia (spo2 $< 94\%$ ) or increased work of breathing , Oxygen by prongs may be provided (Target Spo2 between 94 – 98%) . Patients require  $> 94\%$  saturation during

resuscitation or when acutely ill. At recovery with no tachypnea a saturation of > 90% is enough. In acutely ill patients with spo2 < 94% in spite of oxygen by nasal prongs or with increased work of breathing the options include

- Face mask at > 5LPM flow (Fio2 40-60%): It is not very patient friendly as it interferes with oral feeding and children tend to remove it frequently
- Oxygen hood at > 5LPM flow (Fio2 30 -90%): oxygen hood is an option in newborns and young infants with minimal work of breathing. It provides 90%Fio2 with both ports closed, 60% with 1 port closed and Fio2 30% with both ports open.
- Venturi mask (28-60%Fio2) can provide titrated oxygen with Fio2 ranging from 28% to 60%
- Non rebreathing mask at 10 -15LPM (Fio2 80-90%): it provides high oxygen concentration but not used for long term oxygen administration for risk of oxygen toxicity. It is mainly an interim stabilization measure.

**Heated humidified high flow nasal cannula (HFNC)** may be used preferably over NIV if the target saturation is not achieved with routine 1st line oxygen delivery devices ( nasal prongs, NRM, nasal mask, Venturi , oxygen hood). It should be used only in patients with hypoxemic respiratory failure. It increases the risk of aerosolization but the risk is less than that for NIV.

- Select age appropriate nasal cannula which covers only 50% of the external nares.
- Switch on the machine only after fixing the nasal cannula.
- Start at 0.5 - 1litre per kg per minute and increase up to 2litre /kg/mt if needed.
- Use minimal flow that makes the baby comfortable
- Target spo2 92 - 96%
- Monitor HR and RR. Monitor closely. If no response in 1-2 hours will need escalation of support.
- Flow upto 8l/mt may be used for neonates and upto 25l/mt for children
- An aerosol box covered with surgical mask will help minimize aerosolization while on HFNC

**NIV CPAP/ BIPAP:** It may be offered only in selected patients with hypoxemic respiratory failure. Failure rate with NIV is very high especially in de novo respiratory failure so these patients need close monitoring.

- Use of conventional ventilators for NIV with non vented oro nasal masks / helmets preferable .
- Avoid using dedicated NIV with single limb and vented masks as the risk of aerosolization is very high.
- Connect a bacterial/ viral filter at exhalation port

- Use lowest possible PEEP to achieve targets
- Monitor closely for deterioration and intubate if patient deteriorates or there is no improvement in 1 hour or delivered tidal volume is more than 9.5ml/kg with increased work of breathing as P- SILI may damage the lung further
- Placing of aerosol box with ports covered by surgical mask may decrease risk of aerosolization.

**Mechanical ventilation:** it may be offered to children who do not respond to above respiratory support interventions. Indications include

- Spo2 less than 90%/ P/F ratio less than 150 not responding to above measures
- Severe respiratory distress including high tidal volumes of more than 9.5ml/kg in NIV
- Refractory shock
- Altered mental status with GCS less than 8

### **Airway management**

Airway management should be SAS (safe, accurate, swift). Safe for patient and staff, Accurate, avoiding unfamiliar, unreliable and repeated techniques and Swift i.e timely without rush or delay.

- There is no emergency intubation in pandemic
- Unplanned intubation will harm both patient and health care worker increasing risk of spread of infection and worse outcome.
- Perform intubation only after donning complete PPE
- Limit number of persons present at intubation site to 3. Intubator, assistant and Nurse.
- If facility available intubate in a negative pressure room with > 12 air changes per hour or 160 litres /second / patient in areas with natural ventilation and then shift to main ICU preferably with the same facility to minimise aerosol generation and exposure to others.
- Treatment algorithm and cognitive aids needed like ET tube size, fixing length etc should be displayed in the room.
- All drugs needed should be preloaded preferably outside the room.  
Adrenaline 0.1ml per kg 1 in 10,000 solution  
Atropine 0.02 mg/kg (not needed as routine, use in case of bradycardia or as antispasmodic before ketamine or if using succinylcholine especially repeat dose)  
Ketamine 1- 2mg/kg  
Rocuronium 1. 2mg/kg or succinylcholine 1mg/kg  
Midazolam 0.2mg/kg  
Fentanyl 2mcg/kg or Morphine 0.1mg/kg
- Ensure full neuromuscular blockade before attempting intubation to limit aerosol generation and clamp ET tube before intubation.
- Use aerosol box or intubate under transparent sheet to minimise aerosol generation.
- Fluids and inotropes may be started if hemodynamically unstable before intubation.

- Intubation is preferably performed by the most experienced person to minimise exposure and attempts.
- Preoxygenate preferably allowing spontaneous breathing with NRM , anaesthetic bag or Jackson Rees with face mask for 3 minutes. . Manually bag only if respiratory efforts poor or oxygenation not maintained.
- If bag and mask ventilation needed. Connect HME or bacterial filter to it to limit aerosol generation. Use 2 person 2 handed technique for bagging, one person to hold the face mask tight while the other ventilates to minimise aerosol generation by decreasing leak.
- Video laryngoscope is preferred if available over direct laryngoscope for intubating children with suspected COVID infection.
- Connect ventilator tubings to the ventilator with bacterial / viral filter at exhalation port and set the initial settings beforehand. Inline closed suction and HME filter if being used should also be connected to the tubings beforehand. Post intubation inflate cuff and baby may be directly connected to the ventilator tubings without bagging if possible.
- Check position of ET tube by clinically looking for chest rise , ET co2 if available and check Xray.
- Clean room 20 minutes after aerosol generating procedure or intubation done.
- If intubation failed after 3 attempts 2nd generation supra glottic airways like proseal LMA may be used if available.
- Place NG tube after intubation and ventilation established safely.
- Closed suction preferred over open suction in ventilated pa-ents. Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (eg.transfer to a transport ventilator).
- Post intubation endotracheal sample should be taken for testing if needed (preferred over nasopharyngeal sample).

### **Supportive care**

Keep patient in semi recumbent position and change position every 2 hours. Stress ulcer prophylaxis should be offered with sucralfate or PPI in patients with risk of bleeding. Change heat and moisture exchanger every 5 – 7 days, when it malfunctions or is soiled. Adult HME filters should not be used for small babies as it will increase dead space

### **Initial Ventilator setting**

PCV mode is preferred in children. Titrate Fio2 to target spo2 of 90 - 94% or PaO2 60 - 80 mm of Hg. Pressure support over PEEP or PIP should be kept at a level that delivers tidal volume of 8 ml/kg predicted body weight for height to start with then decrease to achieve 6ml/kg TV if compliance poor. Keep initial PEEP at 6cm later can be titrated.

Ventilation goals

SpO<sub>2</sub> 90 – 94%, pH > 7.3 , P plateau < 28 (<31 if chest wall oedema plus) and driving pressure less than 15 cm H<sub>2</sub>O. If P plateau more than 28, decrease TV to 4-6ml/ kg predicted body weight. TV of 8ml/kg may be acceptable in L type phenotype with normal compliance especially if there is asynchrony or pH less than 7.15.

### Covid 19 pneumonitis

The etiology of Hypoxia in Covid infection is multifactorial. It may be due to ventilation perfusion mismatch due to hyperperfusion of lungs initially followed by pulmonary thrombophlebitis causing pulmonary thrombosis in later stages of disease. Classical ARDS type of lung pathology due to damage to basement membrane and secondary surfactant deficiency is also a cause of hypoxia in certain patients.

### **Identification of type of lung.**

The two types of lung are not mutually exclusive. They often indicate 2 ends of the same spectrum. The lung which initially starts as L type often progresses to H type as the disease progresses. Ventilation strategies differ according to the type of lung. These 2 phenotypes are not mutually exclusive, they may indicate lung in different stages of evolution of disease. Increased work of breathing contributes to lung damage by increasing patient self inflicted lung injury (P- SILI) and is responsible for transition from L Type to H Type (8).

### L type lung

This lung type with good compliance and hypoxia due to ventilation perfusion mismatch is characterized by upright pressure volume loops, attainment of good tidal volumes by low PIP, well aerated lung in USG with A lines.

These patients can be ventilated at 6 – 8ml/kg TV and PEEP 6 – 8cm of H<sub>2</sub>O. If hypoxia persists prone ventilation may be considered. Higher titration of PEEP is not beneficial as amount of recruitable lung is low. Low molecular weight heparin 1mg/kg Sc OD may be started if there is no contraindication and after assessing risk of bleeding.

### H type lung

This is the classical ARDS lung with low compliance characterized by low lying Pressure volume loops, closed flow scalars, need of high pressures to attain 6ml/kg TV. In these patients PEEP may be titrated looking at compliance and hemodynamic status. Refractory hypoxia should be managed with titration of PEEP and prone ventilation of 12 – 16 hrs /day. Recruitment manoeuvres though not routinely recommended may be tried in refractory cases at 30cm of H<sub>2</sub>O for 15 seconds after ensuring absence of air leak and patient should be closely monitored during procedure for hemodynamic compromise.

### Proning

Consider proning if P/F ratio <150 while being ventilated with FiO<sub>2</sub> >0.6 and PEEP >5 cm H<sub>2</sub>O.



Keep prone for 16 -18 hours if possible. Awake proning of older patients on NIV or oxygen support may be considered.

### **Shock**

Any hypotension (systolic blood pressure [SBP] < 5th centile or <70 + age X2 for 1- 10 year old or > 2 SD below normal for age or cold extremities with capillary refill > 3 s and a weak and fast pulse.

- Give 10–20 mL/kg crystalloid (NS/RL/PL) as a bolus in the first 30–60 minutes and reassess for signs of fluid overload after each bolus [1]. If cardiogenic shock is suspected give careful fluid bolus of 5 -10ml/kg over 30mts looking for features of fluid overload like increase in liver size, basal crepitations or worsening respiratory distress.
- Look for evidence of cardiac injury in patients with shock with clinical examination, bedside echo and cardiac enzymes Trop T or trop I.
- Do not use synthetic fluids for resuscitation
- Do not use albumin as the initial fluid for resuscitation.
- Epinephrine or Norepinephrine may be used as the initial inotrope in fluid refractory shock..
- In case of shock with narrow pulse pressure / hypotensive cardiogenic shock adrenaline is preferred.
- In patients with wide pulse pressure shock noradrenaline is preferred.
- Often in MIS-C, LV dysfunction and wide pulse pressure vasoplegic shock coexists , in such situations Noradrenaline with Dobutamine is often found to be useful.
- Further titration depends on hemodynamic parameters like pulse pressure variability, IVC distensibility, lactate clearance, central venous oxygen saturation etc.
- Achieving blood pressure target alone should not be considered as correction of shock. Downstream markers like peripheral perfusion, Urine output, lactate clearance etc are more important.
- In case of catecholamine refractory shock low dose hydrocortisone 2- 4mg/kg/ day may be used as continuous infusion or intermittent dose.

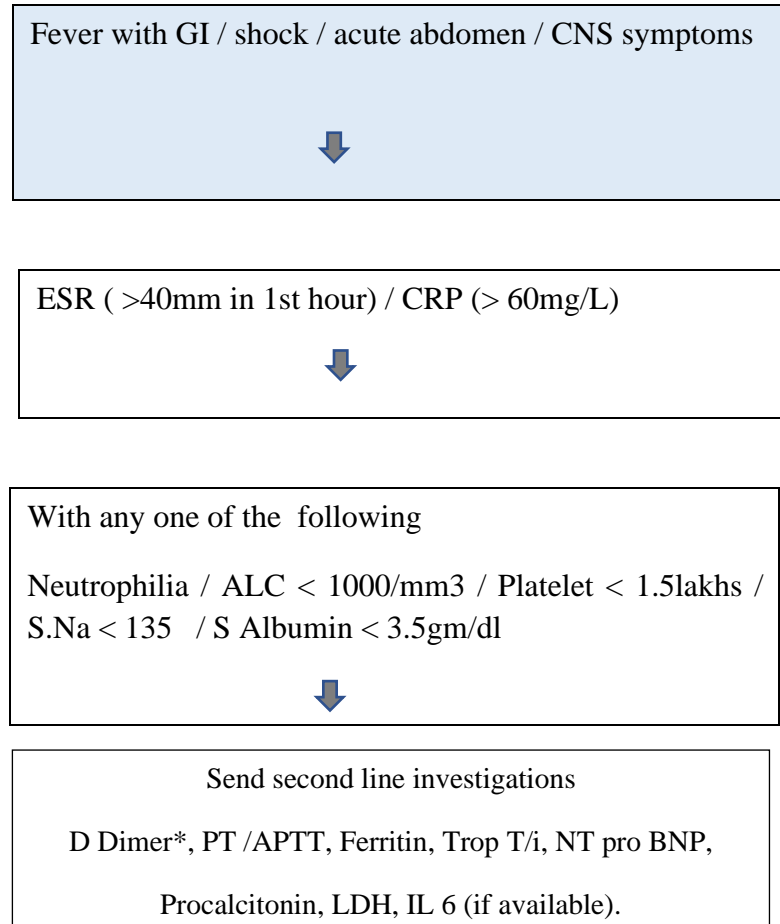
Ivermectin, hydroxychloroquine, tocilizumab and convalescent plasma no more recommended in children with acute covid infection. Remdesivir is also no more recommended by WHO as it did not show any mortality benefit.

### 13. COVID 19 RELATED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

This is a life-threatening complication of SARS COV 2 infection in children which often manifests 3 – 4 weeks after a symptomatic or asymptomatic Covid – 19 infection. Early identification and appropriate treatment is of paramount importance for an optimal outcome. It should be suspected in children presenting with short febrile illness with skin rash, congested mucous membrane, conjunctival congestion or haemorrhage, acute abdomen, shock with evidence of 2 or more organ involvement.

<b>Table 6: Diagnostic Criteria for COVID 19 related MIS-C</b>	
(All of the below needed for diagnosis with no alternate plausible diagnosis)	
Age group	0-19years
Fever	≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours
Symptoms	<p><b>Any 2 of the following</b></p> <ol style="list-style-type: none"> <li>1. Rash / non-purulent conjunctivitis or <b>mucocutaneous</b> inflammation signs (oral, hands or feet).</li> <li>2. Hypotension or <b>shock</b>.</li> <li>3. Features of <b>myocardial</b> dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NTproBNP),</li> <li>4. Evidence of <b>coagulopathy</b> (by PT, PTT, elevated d-Dimers).</li> <li>5. Acute <b>gastrointestinal</b> problems (diarrhoea, vomiting, or abdominal pain).</li> </ol>
Inflammatory markers one or more	Elevated CRP or ESR or Procalcitonin
Evidence of COVID -19 infection	RT-PCR, antigen test or serology positive or likely contact with COVID-19

**Treatment pathway for COVID-19 related Multisystem Inflammatory syndrome in children (MIS-C)**



If no alternate plausible diagnosis treat as MIS-C

*\*Among the second line investigations D dimer and NT Pro BNP are found to be elevated in most patients with MIS-C.*

If all criteria for diagnosing MIS-C are met use any one

IVIG 2gm for kg over 8 -12 hours especially in younger children presenting with Kawasaki Disease like presentation +/- methyl prednisolone 1-2mg/kg/day  
IVIG may be given over longer period of time if evidence of cardiac dysfunction present

Methylprednisolone 30mg /kg/day for 3 days followed by oral prednisolone 2mg per kg per day till CRP normalizes and then taper over 2-3 weeks (Especially preferred in older children presenting in shock)

If fever persists 36 hrs after IVIG -  
Methylprednisolone 30mg /kg/day for 3 days

If fever persists or organ dysfunction does not show significant improvement after treatment with pulse methyl prednisolone (48hrs from start of treatment) IVIG 1-2gm /kg as slow IV infusion.

Aspirin 3-5mg/kg/day  
(If platelet count > 80,000 cells /mm<sup>3</sup> and liver function normal )  
LMW heparin 1mg/kg/ dose BD SC in children with giant aneurysm, Coronary artery aneurysm with Z score > 10 or ejection fraction <35% (factor Xa level 0.5-1)  
Repeat ECG every 48 hours in acute stage

Repeat Echo at 2 weeks , 4 - 6 weeks and @ 1 year ( if initial echo abnormal)  
Aspirin 3-5mg/kg/day  
Can stop at 4weeks if repeat echo normal  
If aneurysm persisting continue till resolution  
Continue LMW heparin (can be changed to warfarin at discharge with monitoring of PT INR ) till thrombus resolution /3 months

Children with MIS-C need periodic follow up to look for resolution of cardiac abnormalities and occurrence of any new symptoms. Cardiac MRI may be considered 4 -6 months after recovery for those who had cardiac dysfunction initially.

## TREATMENT OF MIS-C

Supportive care including correction of shock and respiratory support where needed. Selection and titration of inotrope depending on cardiac contractility, pulse pressure, central venous oxygen saturation and other dynamic measures.

Send for blood and urine culture. Investigations for Dengue, leptospirosis, Scrub typhus may be sent where indicated to look for alternate causes of fever. Repeat ECG every 48 hours and echo needs to be repeated at discharge and at 6 weeks. Organ functions need to be monitored in those with critical illness.

Empiric antibiotic for patients presenting with fever and critical illness (ceftriaxone + clindamycin) Antibiotics may be used according to patients characteristics and local antibiogram

## IMMUNOMODULATION

Immunomodulation is the mainstay of treatment of patients with MIS-C. IVIG and methylprednisolone are the most commonly used immunomodulators in the treatment of IVIG. Robust scientific data from well controlled RCTs are yet not available to determine the optimum therapy. Both IVIG and steroids have shown good response in the treatment of MIS-C.

<b>Persisting fever with high inflammatory markers. No organ involvement or shock.</b>	<b>MIS-C with organ failure or shock</b>	<b>KD phenotype without shock</b>
Rule out alternative cause Methylprednisolone or prednisolone 2mg /kg /day for 5 days	Methylprednisolone 30mg/kg/day X 3 days or IVIG 2gm /kg with methyl prednisolone 2mg/kg/day for 5 days	IVIG 2gm /kg with methyl prednisolone 2mg/kg/day for 5 days
*Aspirin 3-5mg/kg/day x 4weeks	*Aspirin 3-5mg/kg/day x 4weeks	Aspirin* 3-5mg/kg/day x 4weeks
If repeat CRP normal on day 5 decrease to 1mg/kg/day. Taper and stop in 1 week (total 2 weeks). Fever persisting after 72 hours of start of treatment	After MP pulse if fever persists or patient still on inotropes or clinical recovery unsatisfactory	Fever persisting after 36hrs
IVIG 2gm/kg/day or methylprednisolone 10mg/kg/day for 3 days	IVIG 2gm /kg over 12 – 16 hours with methyl prednisolone 2mg/kg/day for 5 days	Methylprednisolone 30mg/kg/day for 3 days taper over 2 to 3 weeks
*Avoid Aspirin if platelet count < 80,000cells/mm <sup>3</sup> . Aspirin needs to be continued beyond 4 weeks if coronary artery changes are persisting. Oral steroids need to be tapered and stopped over 2 to 3 weeks.		

## INTRAVENOUS IMMUNOGLOBULIN (IVIG)

IVIG at a dose of 2g/kg (max. 100gm) with methyl prednisolone 2 mg per kg per day. IVIG is especially preferred in younger patients presenting with KD phenotype.

**Rate of administration:** Start at 0.5 – 1ml/kg/hour then slowly increase to a rate of max. 5ml/kg/hour. Closely monitor for features of fluid overload. For patients with severe LV dysfunction if administration over 8 -12 hours is not feasible due to fluid overload and cardiac dysfunction, it can be given as 1gm /kg/day for 2 days. When feasible IVIG should be given as a single infusion over 8 -12 hrs. Single dose has been found to be superior to divided doses in Kawasaki Disease.

**Adverse effects:** Rash, flu like syndrome (6%), Headache 6-12 hours after infusion (40%), thrombotic event (1 – 17%), aseptic meningitis (0.6-1%), hemolytic anemia (AB group) etc. are some of the reported adverse effects of IVIG. Anaphylaxis following IVIG is very rare, may occur in patients with IgA deficiency with anti IgA antibody.

If after 36 hours of IVIG administration fever persists then methyl prednisolone pulse at a dose of 30 mg per kg (max. 1gm) for 3 days may be offered as the second line therapy.

## IV PULSE METHYL PREDNISOLONE:

MIS-C patients presenting with shock especially in higher age group may be treated with methyl prednisolone pulse 30mg/kg/dose IV daily for 3 days followed by oral Prednisolone 2mg/kg/day until day7 or until CRP normalises and then tapered over 2-3 weeks.

Glucocorticoids have been found to reduce the rate of coronary artery aneurysm in patients with KD at high risk of IVIG resistance [3]. Multiple recent studies have shown that IVIG alone has a high failure rate or longer duration of symptoms and organ dysfunction in MIS-C [6,7]. Most guidelines now recommend IVIG + methylprednisolone 2 mg per kg per day as the 1<sup>st</sup> line therapy in patients with MIS-C .

Experience from published study from Kerala [8] in Indian Pediatrics and from Europe in NEJM[9] shows a modest evidence of efficacy of methylprednisolone alone over IVIG alone. Hence pulse dose methylprednisolone continues to be one of the 1<sup>st</sup> line treatment options in MIS-C in the current Kerala guidelines. As further more robust evidences are gathered the guidelines will be periodically updated.

Given the absence of strong scientific evidence of superiority of one therapy over another, in critically ill children the option of using IVIG or methyl prednisolone pulse therapy as the 1<sup>st</sup> line treatment may be decided by the treating physician.

**Rate of administration:** Methyl prednisolone is administered in normal saline as an infusion over 1 hour.

If fever persists or organ dysfunction does not show significant improvement after methyl prednisolone pulse (48hrs from onset of treatment), IVIG must be offered as a second line therapy. IVIG at a dose of 1-2gm per kg should be given depending on the extent of response to initial methyl prednisolone pulse.

Anakinra (4 – 10mg/kg/day IV or SQ) may be considered for treatment of MIS-C refractory to IVIG and glucocorticoids or in patients with contraindications to these treatments. Children with COVID-19 treated with anakinra should be monitored for liver function test (LFT) abnormalities.

## ANTIPLATELET AND ANTICOAGULATION

### ASPIRIN

Patients with MIS-C are at risk of developing thrombotic complications including apical ventricular thrombus, pulmonary embolism and coronary thrombosis.

Low dose Aspirin at 3-5mg/kg/day (max 75mg) should be given to all patients with MIS-C and continued for 4-6 weeks until normalization of platelet count and confirmed normal coronaries at  $\geq 4$  weeks

Aspirin needs to be continued till resolution of coronary artery changes. Patients with Coronary artery aneurysm (CAA) more than 10 Z score need indefinite treatment.

Treatment with Aspirin should be avoided in patients with a platelet count  $\leq 80,000/\mu\text{L}$  (M). Avoid Aspirin in acute phase if evidence of liver failure.

### Therapeutic Anticoagulation

Low molecular weight Heparin 1mg per kg BD SC (factor XA level 0.5 -1). These patients at discharge may be transitioned to warfarin with monitoring of PT INR

Indications	Contraindications
Documented thrombosis	Active bleed / IC Hemorrhage
Ejection fraction (EF) <35%	Thrombocytopenia (< 50,000)
CAA > 10 Z score.	LP / Neurosurgery procedure in 24 hours
	PT INR > 1.8

Duration of anticoagulation:

- At least 2 weeks after discharge from the hospital.
- If thrombus persists then 3 months or more till thrombus resolution.
- CAA with z-score >10.0 (indefinite treatment)
- Ongoing moderate to severe LV dysfunction (longer duration)

### Prophylactic anticoagulation

Prophylactic anticoagulation with low molecular weight Heparin 0.5mg/kg BD or 1mg /kg OD (anti Xa level 0.2 to <0.5 U/mL ) may be offered to patients admitted with MIS-C without severe renal impairment and who are at increased risk of thrombosis. Indications for prophylactic anticoagulation in admitted patients include-

- D Dimer > 5times upper limit of normal,
- Patients with central lines and two or more risk factors
- Previous history of thrombosis / family history of thrombosis
- 4 or more risk factors

<b>Table 6: Risk factors for thrombosis</b>	
Children above 12 years of age	mechanical ventilation
inotropic support	Obesity
Congenital or acquired heart disease with venous stasis	Post splenectomy for underlying haemoglobinopathy
active malignancy	cystic fibrosis exacerbation
sickle cell vaso occlusive crisis	Nephrotic syndrome

### **MILD MIS-C / FEBRILE HYPERINFLAMMATORY SYNDROME**

Patients with high inflammatory markers with fever without evidence of organ failure, shock, coronary involvement or any life-threatening condition, should be closely monitored for new onset symptoms and signs of organ involvement. Attempt should be made to identify an alternative cause of fever. If there is no alternative diagnosis and patient fulfills criteria for MIS-C, they should be treated with Inj. methylprednisolone or oral prednisolone 2 mg/kg/day.

Taper and stop steroids over 2 weeks monitoring inflammatory markers especially CRP. Repeat CRP on day 5 if normal, steroid may be decreased to 1mg/kg/day and tapered over next 1 week. Usually 2 mg per kg per day is continued till CRP normalizes and then dose is tapered. Aspirin at anti platelet dose (3-5mg/kg/day) may be started with reassessment with echo at 4 weeks. If coronaries normal at 4 weeks it can be stopped. If patient does not respond to steroids, IVIG 2 gm per kg or methylprednisolone pulse with 10mg/kg /day for 3 days (max.1gm) may be given. A proportion of children with febrile inflammatory syndrome may show clinical resolution of signs and symptoms without any immunomodulatory treatment.

### **Follow UP**

Children with MIS-C require periodic follow up.

Repeat Echo at discharge / 2 weeks and 6 weeks. In case of persistent coronary artery dilatation or cardiac dysfunction periodic follow up with echocardiography will be required.

Aspirin may be stopped once coronary artery changes normalizes.

Cardiac MRI may be done after 4 - 6 months in patients with history of cardiac dysfunction to look for functional assessment, T1 mapping and extracellular volume (ECV) quantification and late gadolinium enhancement.

Cardiac CT may be performed in patients with suspicion of distal CAAs that are not well seen on echocardiogram.



*NB: Protocol will be modified as new evidences are gathered.*

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#### 14. MIS-A [Multi system inflammatory syndrome in Adults]

Adult patients of all ages with current or previous SARS-CoV-2 infection can develop a hyperinflammatory syndrome resembling MIS-C. Although hyperinflammation and extrapulmonary organ dysfunction have been described in hospitalized adults with severe COVID-19, these conditions are generally accompanied by respiratory failure. In contrast, the patients with MIS-A have minimal respiratory symptoms, hypoxemia, or radiographic abnormalities. Hypoxemia observed in MIS-A is usually due to cardiogenic pulmonary edema due to myocarditis. This aspect helps to distinguish MIS-A from severe COVID-19.

The clinical features of multisystem inflammatory syndrome in adults (MIS-A) present some time (usually weeks) after COVID-19 infection, so the diagnosis of COVID-19 may not be elicited and swabs for SARS-CoV-2 are expected to be negative. The clinical presentation is often acute severe abdominal pain with diarrhoea or high grade unremitting fever treated as sepsis refractory to antibiotics. MIS-A progresses with hyperinflammation leading to devastating cardiogenic shock. Key laboratory features may include raised inflammatory markers such as C-reactive protein, raised ferritin (>500), raised fibrinogen, and raised troponin and NT-pro-BNP. The full blood count may or may not be abnormal with lymphopenia, neutrophilia or thrombocytopenia. These tests may change rapidly and should be monitored daily. If recognised and treated promptly with high-dose immunosuppression these adults may go on to make a full recovery. There is no current evidence base to guide immune suppression but steroids and biologic drugs are currently used. Diagnosis of MIS-A requires high index of suspicion. If diagnosis is missed, outcome may be bad.

Working MIS-A case definition includes SIX criteria:

1. A severe illness requiring hospitalization in a person aged  $\geq 21$  years;
2. A positive test result for current or previous SARS-CoV-2 infection (nucleic acid, antigen, or antibody) during admission or in the previous 12 weeks;
3. Severe dysfunction of one or more extrapulmonary organ systems (e.g., hypotension or shock, cardiac dysfunction, arterial or venous thrombosis or thromboembolism, encephalitis, colitis or acute liver injury);
4. Laboratory evidence of severe inflammation (e.g., elevated CRP, ferritin, D-dimer or IL-6)
5. Absence of severe respiratory illness (to exclude patients in which inflammation and organ dysfunction might be attributable simply to tissue hypoxia). Patients with mild respiratory symptoms who met these criteria were included.
6. Absence of alternative diagnosis like septic shock, Tropical fever syndromes, infective

Approximately 70% of patients with MIS-A have lab evidence of current or post COVID-19 (PCR or serology). Patients may have suspected exposure to COVID-19 case 3-4 weeks prior to MIS-A illness. Maintain higher index of suspicion in patients with history of COVID -19 in the household or locality.

#### CDC classification of MISA

- ▶ Age >21 yrs subjective or documented fever >38 c for 24 hrs prior to or within 3 days of hospitalisation
- AND
- ▶ SARS COV 2 positive RT-PCR/antigen/serology
- AND
- ▶ Lab evidence of inflammation 2 of the following-crp,ferritin,esr,IL6, procalcitonin
- AND
- ▶ Hospitalized more than 24 hrs
- AND
- ▶ 3 of the following within 3 days of hospitalisation (one must be primary)
- ▶ Primary-
  - cardiac illness
  - rash
  - non purulent conjunctivitis
- ▶ Secondary
  - new onset neurological- encephalopathy , cognitive disturbance, seizures, meningeal signs, neuropathy
  - shock or hypotension not attributable to medical therapy (sedation, RRT)
  - abdominal pain, vomiting, diarrhea
  - platelets < 1.5 lacs

#### Rule of the thumb

Suspect MIS-A in any patient with leucocytosis , neutrophilia and myocarditis presenting with

1. Fever, acute abdominal pain, diarrhea ± hypotension
2. High grade unremitting fever ± hypotension.

## Treatment

There are NO standardized treatment protocols for MIS-A. The immunomodulators tried are

1. Inj Methyl prednisolone 25mg/kg/day loading dose followed by 20 mg/kg/day for 5 days and then steroid taper.
2. IVIg 2g/kg
3. In refractory cases, Anakinra or Tocilizumab may be administered.

## 15.COVID ASSOCIATED PULMONARY ASPERGILLOSIS [CAPA]

Severe acute respiratory syndrome coronavirus 2 causes direct damage to the airway epithelium, enabling aspergillus invasion. Reports of COVID-19-associated pulmonary aspergillosis have raised concerns about it worsening the disease course of COVID-19 and increasing mortality. CAPA is emerging as a serious secondary infection in patients with COVID-19 and ARDS, and two studies have indicated excess mortality rates of 16% and 25% compared with patients without evidence for aspergillosis.

### CLINICAL DEFINITION OF CAPA

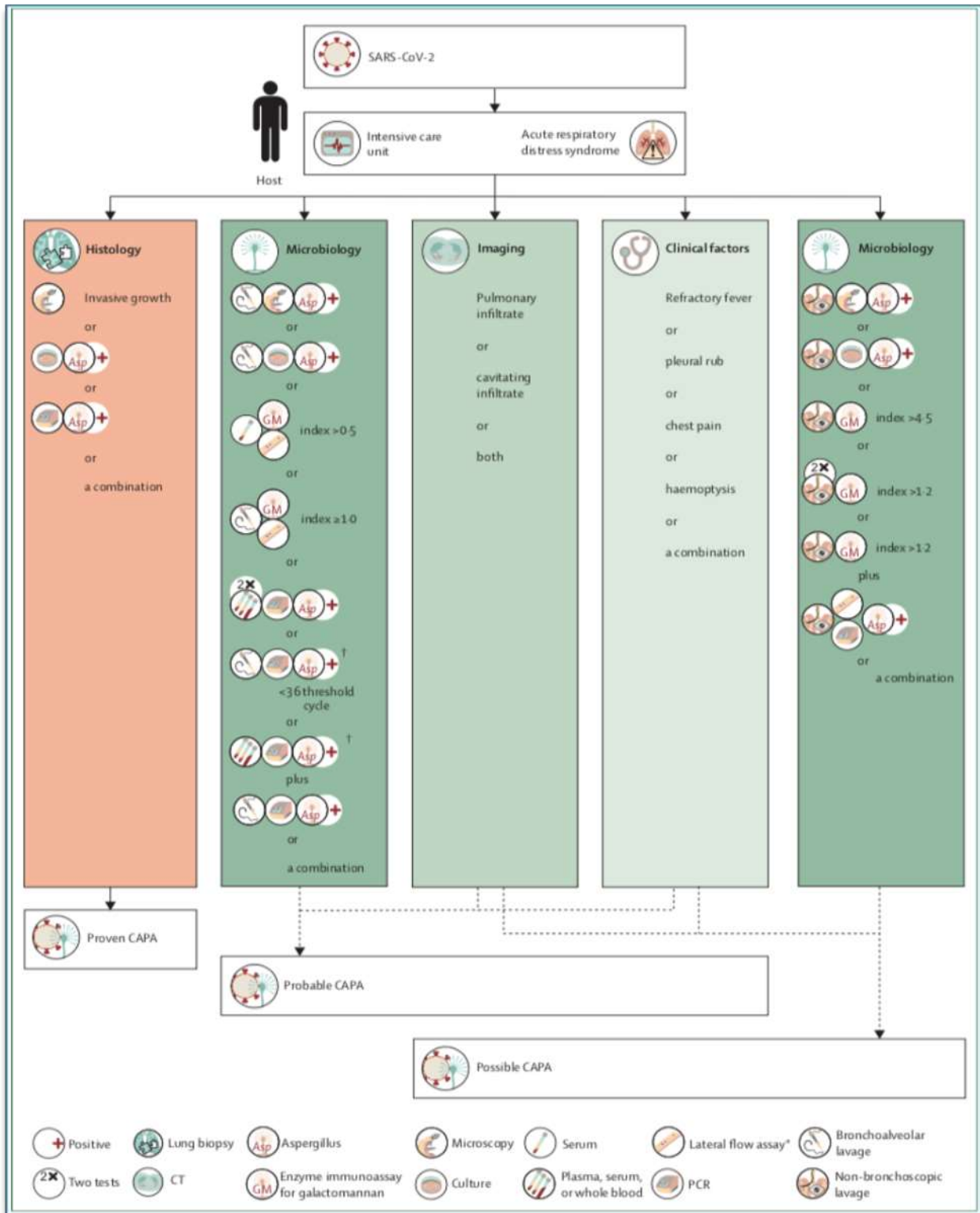
Proposed case definition for CAPA (adapted from EORTC and MSGERC <sup>3</sup> , AspiCU <sup>17</sup> , and expert case definitions of IAPA <sup>18</sup> )			
Tracheobronchitis or other pulmonary form (proven)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)		At least one of the following: histopathological or direct microscopic detection of fungal hyphae, showing invasive growth with associated tissue damage; or aspergillus recovered by culture or microscopy or histology or PCR obtained by a sterile aspiration or biopsy from a pulmonary site, showing an infectious disease process
Tracheobronchitis (probable)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Tracheobronchitis, indicated by tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis	At least one of the following: microscopic detection of fungal elements in bronchoalveolar lavage, indicating a mould; positive bronchoalveolar lavage culture or PCR;† serum galactomannan index >0.5 or serum LFA index >0.5;‡ or bronchoalveolar lavage galactomannan index ≥1.0 or bronchoalveolar lavage LFA index ≥1.0†
Other pulmonary forms (probable)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Pulmonary infiltrate, preferably documented by chest CT, or cavitating infiltrate (not attributed to another cause)	At least one of the following: microscopic detection of fungal elements in bronchoalveolar lavage, indicating a mould; positive bronchoalveolar lavage culture;† serum galactomannan index >0.5 or serum LFA index >0.5;‡ bronchoalveolar lavage galactomannan index ≥1.0 or bronchoalveolar lavage LFA index ≥1.0;‡ two or more positive aspergillus PCR tests in plasma, serum, or whole blood;† a single positive aspergillus PCR in bronchoalveolar lavage fluid (<36 cycles);† or a single positive aspergillus PCR in plasma, serum, or whole blood, and a single positive in bronchoalveolar lavage fluid (any threshold cycle permitted)†
Other pulmonary forms (possible) <sup>19,5</sup>	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Pulmonary infiltrate, preferably documented by chest CT, or cavitating infiltrate (not attributed to another cause)	At least one of the following: microscopic detection of fungal elements in non-bronchoscopic lavage indicating a mould; positive non-bronchoscopic lavage culture;† single non-bronchoscopic lavage galactomannan index >4.5; non-bronchoscopic lavage galactomannan index >1.2 twice or more; or non-bronchoscopic lavage galactomannan index >1.2 plus another non-bronchoscopic lavage mycology test positive (non-bronchoscopic lavage PCR or LFA)

## PROS AND CONS OF DIAGNOSTIC PROCEDURES

	Pros	Cons	Comments related to CAPA
Lung biopsy	Provides proof of IPA	Risk of sampling error; scarcely used due to high risk of complications	CT-guided biopsies post mortem have been used as alternative to autopsy <sup>23</sup>
Bronchoscopy with bronchoalveolar lavage	Allows visualisation of lesions (eg, plaques); bronchoalveolar lavage well validated for the diagnosis of IPA and IAPA; validated specimen for aspergillus antigen test (eg, enzyme immunoassay and lateral flow assay) and PCR; targeted sampling possible	Aerosol generation and contamination of surfaces	In some centres, use is decreased because of risk of nosocomial transmission and SARS-CoV-2 infection of health-care workers; <sup>27,30</sup> SARS-CoV-2 infectiousness correlates with PCR-signal strength, which can be used as guidance on when it's safe to perform bronchoscopy <sup>31-33</sup>
Non-bronchoscopic lavage	Obtains material from lower respiratory tract; technique validated for diagnosis of ventilator-associated pneumonia; closed-system sampling	Not fully validated for IPA diagnosis; not fully validated for aspergillus antigen and PCR detection; non-targeted sampling	Suggested as alternative to bronchoalveolar lavage to diagnose CAPA; small number of validation studies <sup>22,34</sup>
Tracheal aspirate	Easy to obtain in patients who are intubated	Less representative of lower respiratory tract than is bronchoalveolar lavage; not validated for biomarker detection	Often positive in patients with COVID-19 who are critically ill but can represent upper airway colonisation
Sputum	Easy to obtain in most patients	Less representative of lower respiratory tract than is bronchoalveolar lavage; not validated for biomarker detection	Often positive in patients with COVID-19 who are critically ill but can represent upper airway colonisation
Serum	Highly indicative for IPA (galactomannan, lateral flow assay, and PCR); validated specimen for galactomannan, lateral flow assay, (1-3)-β-D-glucan, and PCR; easy to obtain	Variable performance in non-neutropenic patients; (1-3)-β-D-glucan not pathogen specific	Commonly negative in CAPA, including proven cases <sup>21</sup>

CAPA=COVID-19-associated invasive pulmonary aspergillosis. IAPA=influenza-associated pulmonary aspergillosis. IPA=invasive pulmonary aspergillosis.

# DEFINING AND DIAGNOSING CAPA

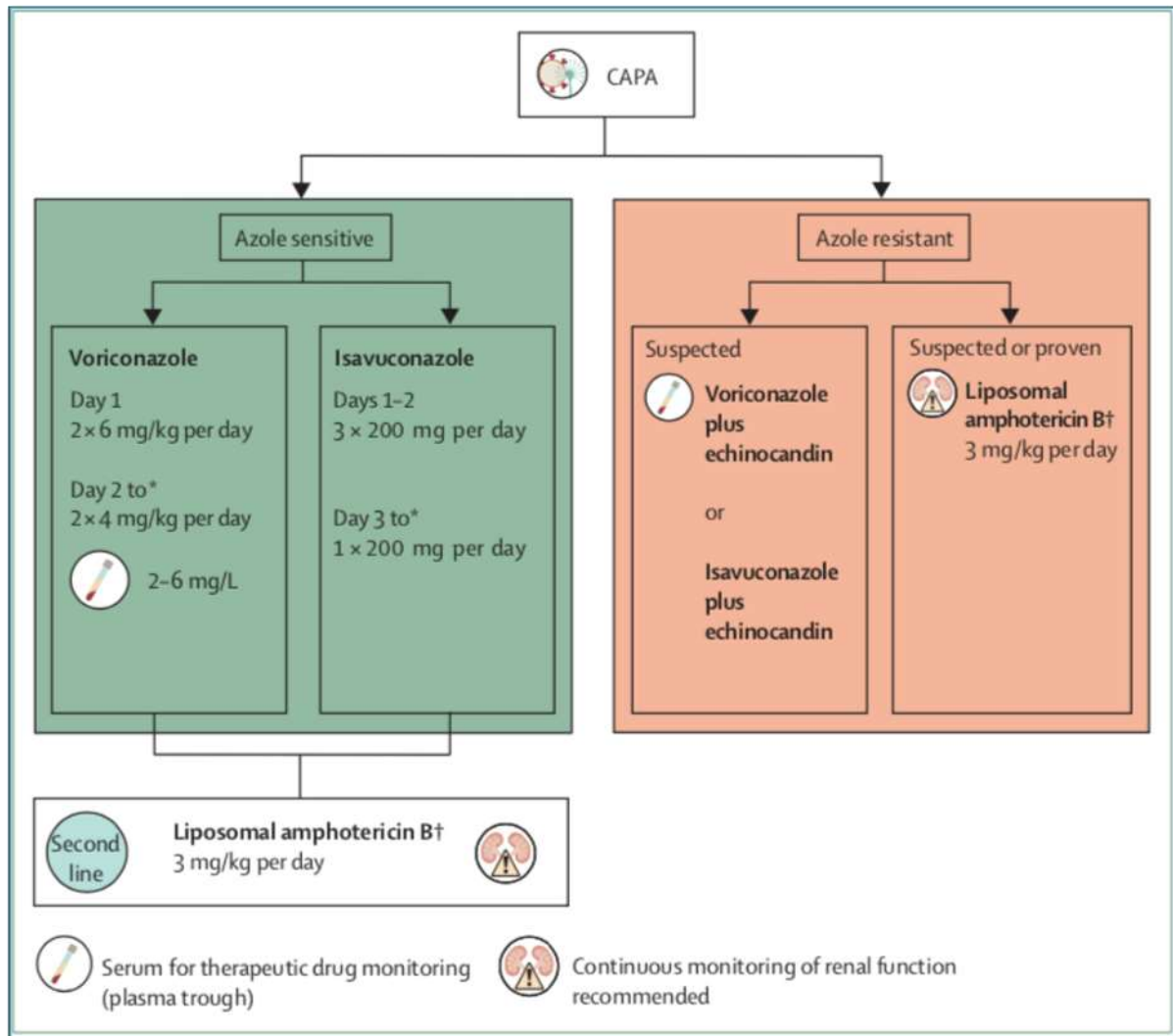




## TREATMENT

1. For the treatment of possible, probable or proven CAPA, the preferred agents for first line treatment are either Voriconazole or Isavuconazole.
2. The route of administration should preferably be intravenous, due to possible malabsorption from gastroparesis in patients in intensive care units.
3. Voriconazole treatment (loading dose 6 mg/kg twice a day for two doses, followed by 4 mg/kg twice a day) has a better outcome than does treatment with Amphotericin B Deoxycholate, especially with its known serious toxicities. However, liposomal Amphotericin B can be considered for initial therapy if, epidemiologically, drug-resistant patterns support this treatment, before the results of susceptibility testing for Voriconazoles are available. The recommended initial dose of liposomal Amphotericin B is 3 mg/kg per day.
4. Daily Isavuconazole treatment (loading dose 200 mg three times a day for six doses, followed by 200 mg once a day, 12–24 h after the last loading dose) has similar clinical activity to Voriconazole but less hepatotoxicity and neurotoxicity and decreased risk of corrected QT-interval prolongation.
5. Echinocandins are not recommended for use as monotherapy in primary invasive aspergillosis; but, in combination with an azole, might have some therapeutic advantage in critically ill patients and in areas of high prevalence of azole resistance because combination therapy can broaden the coverage until minimal inhibitory concentrations become available.
6. Posaconazole has excellent in-vitro aspergillus activity and has been successfully used as salvage treatment in patients without COVID-19.
7. Itraconazole shows excellent in-vitro aspergillus activity but does not have robust comparative data with established regimens.
8. For azole resistant strains, polyene therapy is suggested.
9. The optimal duration of therapy is unknown and radiological lung imaging might not be a helpful gauge. Usual duration of antifungal treatment is 6–12 weeks. However, it seems reasonable to include follow-up lung CT imaging to document the resolution of infiltrates before termination of treatment. In patients who are immunocompromised (eg, with haematological malignancy or receiving immunosuppressive therapy), longer treatment might be necessary than for other patients. Following the galactomannan-index in serum as a measure of therapeutic response might be limited by its poor sensitivity when testing serum in non-neutropenic patients, but attaining follow-up respiratory samples for galactomannan testing could be useful to determine efficacy in patients who are galactomannan positive, which might help to determine treatment duration.

## RECOMMENDED TREATMENT FOR CAPA



Reference: *Lancet Infect Dis* 2021; 21: e149–62 Published Online December 14, 2020 [https://doi.org/10.1016/S1473-3099\(20\)30847-1](https://doi.org/10.1016/S1473-3099(20)30847-1)

## **16. Technical Guideline on diagnosis and treatment of COVID 19-associated mucormycosis (CAM)**

Since the onset of the COVID 19 pandemic there have been multiple reports across India of very high incidence of mucormycosis among patients with COVID 19 especially in those who are diabetic and those who have received steroids and immunosuppressants like Tocilizumab. Even though CAM has been reported from Kerala also over last 6 months, the number of cases reported is below the background rate of invasive mucormycosis reported in Immunocompromised especially those with uncontrolled diabetes in the preceding years. Since development of CAM is closely linked to glycemic status, a chapter on optimization of glycemic status in diabetic patients with concomitant COVID 19 infection has been incorporated into version 3 of Kerala State Guidelines on Treatment of Covid 19. A video module of the same has been prepared and circulated for IEC.

Covid-associated mucormycosis (CAM) is associated with high morbidity and mortality, exorbitant treatment costs and has led to shortage of antifungal drugs. Mucormycosis is a diabetes-defining illness, and remains as one of the most devastating complications in uncontrolled diabetics with mortality rates ranging between 40-80%. India contributes to 40% of the global burden of mucormycosis, with an estimated prevalence of 140 cases per million population. Single most risk factor for development of invasive mucormycosis is uncontrolled glycemic status. Studies have revealed that 47% of Indians are unaware of their diabetic status and only a quarter of diagnosed cases have achieved adequate glycemic control on treatment.

### **Pathogenesis of COVID 19-associated mucormycosis [CAM]**

Unlike Covid associated pulmonary aspergillosis [CAPA], invasive mucormycosis has been observed even in patients with mild to moderate SARS- CoV-2 infections. The strongest predisposing factor appears to be hyperglycemia in undiagnosed or uncontrolled in patients with diabetes. Hyperglycemia leads to increased expression of the endothelial receptor GRP78, resulting in polymorphonuclear dysfunction, impaired chemotaxis and defective intracellular killing. An important virulence trait of Mucorales is the ability to acquire iron from the host which is an essential element for its growth. In conditions of ketoacidosis, free iron becomes readily available in the serum. This excess endogenous iron is efficiently taken up by the Mucorales through siderophores or iron permeases, further enhancing their virulence. These effects are greatly amplified by the use of corticosteroids and immunosuppressants in susceptible hosts. Corticosteroids themselves cause impairment in the neutrophil migration, ingestion, and phagolysosome fusion. Coupled with the potential implications of steroid-induced hyperglycemia, the COVID 19 patients with diabetes receiving corticosteroids or other immunosuppressants are exceptionally vulnerable to the development of mucormycosis.

## When and how to suspect CAM

CAM –can occur along with active COVID 19 infection [concomitant] and can occur sequentially in weeks or months following recovery [sequential]

CAM based on clinical presentation is classified as

1. Rhino-orbito-cerebral mucormycosis [ROCM]
2. Pulmonary mucormycosis.
3. Gastrointestinal mucormycosis –rarely seen in neonates.
4. Disseminated mucormycosis-seen in the setting of diabetic ketoacidosis or severe immunosuppression.
5. Primary cutaneous mucormycosis

Common presentation of ROCM

- Initially – nasal blockade or congestion, nasal discharge (bloody or brown/ black), local pain
- Facial pain or numbness or swelling, palpebral swelling, conjunctival congestion, ptosis, extraocular muscle involvement.
- Headache, orbital pain ,loss of vision
- Toothache, loosening of maxillary teeth, jaw involvement
- Blurred or double vision with pain; paresthesia, fever, skin lesion, thrombosis & necrosis (eschar)

### **Warning symptoms and signs of Rhino-orbito-cerebral mucormycosis**

- Nasal stuffiness
  - Foul smell
  - Epistaxis
- Nasal discharge - mucoid, purulent, blood-tinged or black
- Nasal mucosal erythema, inflammation, purple or blue discoloration, white ulcer, ischemia, or eschar
  - Eyelid, periocular or facial edema
  - Eyelid, periocular, facial discoloration
- Regional pain – orbit, paranasal sinus or dental pain
  - Facial pain
  - Worsening headache
  - Proptosis
  - Sudden loss of vision
- Facial paresthesia, anesthesia
  - Sudden Ptosis
- Ocular motility restriction, diplopia
  - Facial palsy
- Fever, altered sensorium, paralysis, focal seizures

### **Pulmonary mucormycosis:**

- Fever, cough, chest pain, pleural effusion, hemoptysis, worsening of respiratory symptoms
- Lung CT – suspect mucormycosis in patients with thick-walled lung cavity (need to differentiate from covid-associated pulmonary aspergillosis), reverse halo sign, multiple nodules, pleural effusion .Presence of reverse halo sign [Atoll sign],more than 10 pulmonary nodules and pleural effusion is more in favour of CAM than CAPA. Presence of bronchial thickening, tracheobronchial involvement, peribronchial collection and tree in bud nodules are more in favour of CAPA.Tuberculosis has to be ruled out by appropriate tests.
- Serum and BAL Galactomannan and beta D glucan tests are negative in CAM and usually will be positive in CAPA.

Mucormycosis is a medical emergency and in correct context should be started on empirical therapy even prior to diagnostic confirmation.

Suspected patients should undergo appropriate radio-imaging study at the earliest. MRI - PNS with brain contrast study for ROCM and plain CT thorax for pulmonary mucormycosis must be done. Diagnosis is confirmed by fungal staining /culture from appropriately collected specimens.

#### Rhino-orbito-cerebral

- Consult ENT surgeon for endoscopic collection of debrided tissue/biopsy – one portion in sterile saline for microscopy & culture, other portion in formalin saline for histopathology

#### Pulmonary

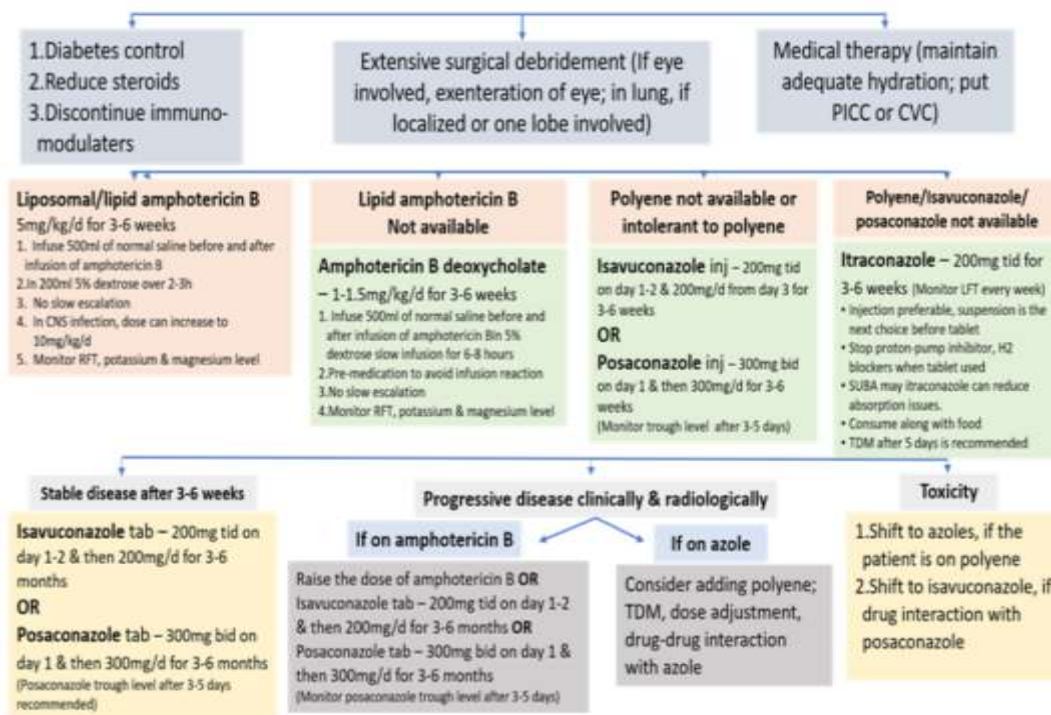
- Broncho-alveolar lavage (BAL), Mini BAL, non-bronchoscopic lavage, transbronchial biopsy, CT guided biopsy from lung – process for microscopy & culture
- Chest X-ray and/ or HRCT – reverse halo sign, thick-walled cavity (need to differentiate from Covid associated pulmonary aspergillosis), multiple nodules, pleural effusion

### Treatment of CAM

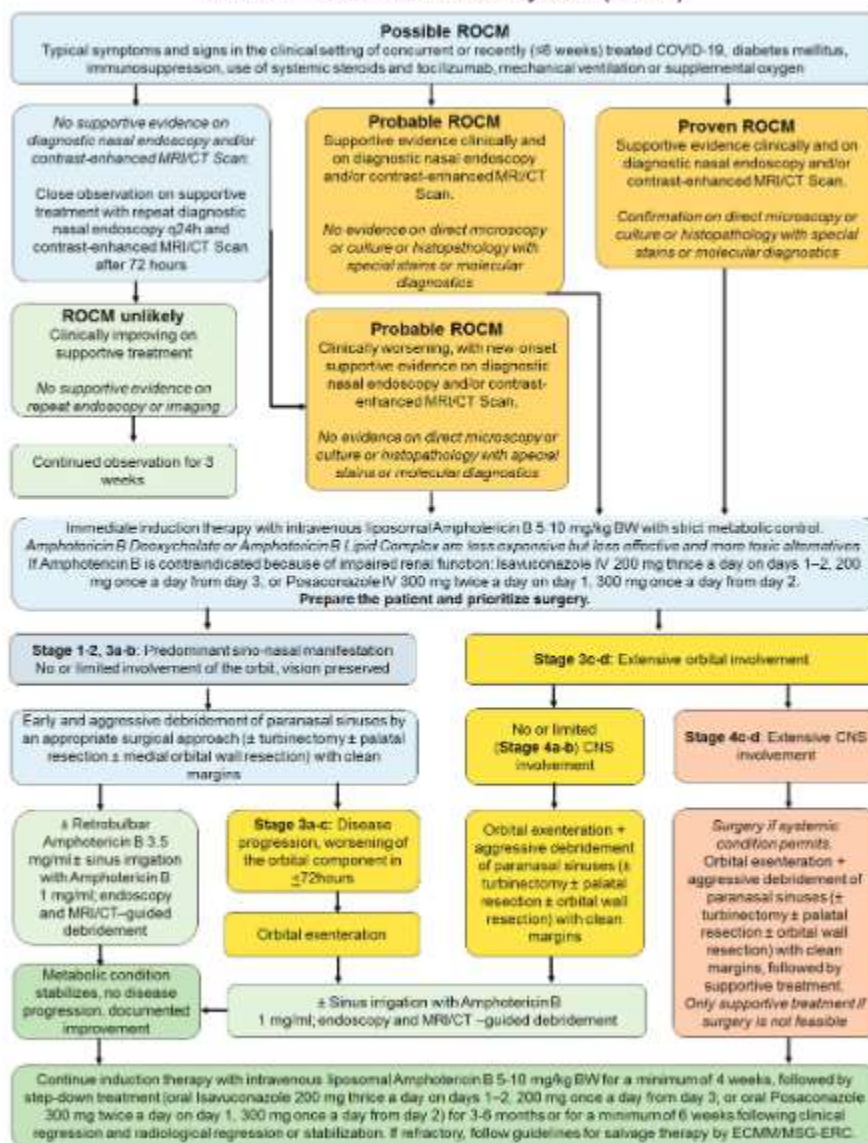
Team approach is required with Physician, infectious disease specialist, microbiologist, histopathologist, intensivist, neurologist, ENT specialist, ophthalmologist, dentist, surgeons, radiologists etc.

1. Control of diabetes & diabetic ketoacidosis
2. Reduce steroids (if patient is still on) with aim to discontinue rapidly
3. Discontinue other immunomodulating drugs if patient is taking like: Baricitinib, Tofacitinib
4. Surgical debridement: Extensive surgical debridement must be done to remove all necrotic material. Antifungal penetration into necrotic tissue is sub-optimal. Involved eye may have to be exenterated as per opinion of ophthalmologist.
5. Medical treatment
  - a. Insert peripherally inserted central catheter (PICC line) or central venous catheter
  - b. Maintain adequate systemic hydration, infuse normal saline IV before amphotericin B infusion
  - c. Antifungal therapy
    - i. Liposomal amphotericin B (L-AmB) (preferred treatment) 5mg/kg/day, dilute in 200 cc 5% dextrose over 2-3 hours infusion (avoid slow escalation; higher dose 10mg/Kg/day may be given in brain involvement)

- ii. Amphotericin B deoxycholate (D-AmB): only if cost and availability of L-AmB is an issue; 1mg/kg/day in 5% dextrose, slow infusion for 6-8 hours at rate of 0.08 mg/kg/hour. Pre-medication may be required to avoid infusion reaction. Pre-loading with 1 L NS in patients without risk of fluid overload, and administering 1L NS after infusing Amphotericin will help in limiting nephrotoxicity.
- iii. Monitor renal function & potassium level while treating with amphotericin B. If hypokalemia is not getting corrected with intravenous potassium chloride, hypomagnesemia should be ruled out.
- iv. Patients who are intolerant to amphotericin B, alternative agents are posaconazole or isavuconazole (injection/tablets). Posaconazole is also available as syrup formulation.
  - v. Tab/intravenous posaconazole: 300mg twice a day on first day, followed by 300mg once a day. Check posaconazole trough level after 7 days of therapy [if TDM-Therapeutic drug monitoring is available] & check for drug interaction.
  - vi. Tab/intravenous isavuconazole: 200mg three time a day for two days, followed by 200 mg once a day.
6. Monitor patients clinically, microbiologically and with radio-imaging for response / disease progression.
7. After 3-6 weeks of amphotericin B therapy, consolidation therapy with (posaconazole/isavuconazole) for 3-6 months should be instituted. Duration of therapy depends on clinical response and radiological resolution and has to be individualized.



## Management Approach for Possible, Probable or Proven Rhino-Orbito-Cerebral Mucormycosis (ROCM)



## How to prevent COVID associated Mucormycosis

- As poorly controlled diabetes is the major issue, good glycaemic control during management of COVID 19 patients is required.[Refer Optimization of Glycaemic status in patients with diabetes and COVID 19: Chapter 13: Kerala State COVID 19 treatment guidelines Version 3]
- Systemic /oral steroids should be administered only as per indications mentioned in: Kerala State COVID 19 treatment guidelines Version 3.
- Glycaemic control should be optimized in all patients especially when started on steroids.
- In all patients with diabetes, best way to prevent CAM is by optimizing glycaemic status as cases of CAM have been reported even without exposure to steroids.



- All patients at risk of developing mucormycosis those with uncontrolled diabetes mellitus, chemotherapy, post-transplant, long term steroids and those with COVID 19 moderate to severe disease should ideally avoid construction sites. As air near construction sites will be full of fungal spores and the Immunocompromised are at risk of developing COVID associated pulmonary aspergillosis [CAPA] and CAM.
- Universal masking reduce exposure to Mucorales and hence should be strictly practiced.
- Strict aseptic precautions while administering oxygen must be adhered to like sterile water for humidifier, daily change of sterilized humidifier and the tubes].
- During discharge of the patients, advice about the early symptoms or signs of mucormycosis (facial pain, nasal blockage and excessive discharge, loosening of teeth etc., chest pain, respiratory insufficiency) and to report to the treatment facility.
- Aeromycological study to assess the presence and to quantify Fungal spore count should be done periodically in all ICUs.

1. Mucorales are not black fungi. Black fungi are different category of fungi having melanin in the cell wall.
2. Mucormycosis is not contagious. It does not spread from one person to another.
3. Mucormycosis is not spread by oxygenation, humidifier, and water. The fungi remain in the indoor & outdoor environment. The spores enter the respiratory tract via air.
4. No antifungal prophylaxis is recommended as the incidence is not more than 10% in any COVID-19 cohort.

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## **17.OPTIMIZATION OF GLYCAEMIC STATUS IN PATIENTS WITH DIABETES AND COVID 19**

### **BACKGROUND**

It has been observed during State death audit that in patients with COVID 19 and diabetes mellitus, uncontrolled glycaemic status at presentation and dysglycemia during treatment are associated with adverse clinical outcomes. It is in this regard that this advisory has been prepared with regard to optimization of glycaemic status in patients with diabetes and COVID -19, with the aim of further reducing case fatality rate in Kerala. This evidence-based advisory has been prepared by Department of Endocrinology, GMC Thiruvananthapuram.

### **INTRODUCTION**

A bidirectional relationship exists between COVID 19 and Diabetes mellitus. The presence of Diabetes mellitus has been identified as a strong risk factor for increased COVID-19 disease severity and worse outcomes, including higher mortality. A recent multicentric study identified that the odds for in-hospital deaths with COVID-19 were 3.51 (95% CI 3.16–3.90) for people with type 1 diabetes and 2.03 (1.97–2.09) for people with type 2 diabetes compared with non-diabetic patients after adjusting for the major confounders.

The interplay between COVID-19 and Diabetes entails a complex pathophysiology. Presence of hyperglycemia increases the risk of COVID morbidity and mortality by the following mechanisms – increased cellular binding and efficient viral entry via upregulation of ACE2 receptor, decreased viral clearance, reduced T cell function and increased susceptibility to hyperinflammation and cytokine storm. COVID 19 infection has a diabetogenic effect well beyond the stress response associated with severe illness. Once the infection is established, glycaemic control gets worsened due to the systemic inflammatory state with increased catecholamine and glucocorticoid levels compounding insulin resistance, direct cytopathic effect on beta cells of pancreas impairing insulin secretion and increased rate of formation of glycation end products. The use of glucocorticoids for severe infection further worsens the glycaemic status. Insulin requirement rises manifold and there is increased risk of precipitation of hyperglycaemic emergencies like Diabetic Ketoacidosis and Hyperosmolar Hyperglycaemic state. Optimal management of dysglycemia is of paramount importance to improve the clinical outcomes and decrease the morbidity and mortality associated with COVID infection in patient with Diabetes mellitus.

### **Management of Diabetes mellitus in COVID infection**

#### **Evaluation in all patients**

- RBS, FBS/PPBS, HBA1C
- If already diagnosed with Diabetes mellitus

- Type and duration of diabetes
- Details of OHA / Insulin treatment
- Serum creatinine
- History of hypoglycemia / hyperglycemic emergencies.
- Tests to be done using a calibrated glucometer

**Part 1: Screening and Monitoring**

	<b>A</b>	<b>B</b>	<b>C</b>	<b>E</b>	<b>F</b>
	<b>COVID CAT A</b>	<b>COVID CAT B</b>	<b>COVID CAT C / ON STEROIDS</b>	<b>NASOGASTRIC FEEDS</b>	<b>ON PARENTERAL NUTRITION ONLY</b>
<b>Non-Diabetic</b>	RBS only, if less than 140 no further test, if more, – FBS PPBS and Hba1c if found diabetic see cell B2	FBS, 2 hr post Breakfast, Hba1c	FBS, 2 hr Post breakfast, Hba1C	Fasting, 2 hr post feeds	6 hourly RBS
<b>Diabetic with reasonable control on admission (FBS&lt;140 mg%, PPBS &lt;180 mg% Hba1c &lt;8 %)</b>	FBS, Post Breakfast, Hba1c on admission  FBS , PPBS every 3 days	FBS, Post Breakfast, Hba1c on admission  FBS , PPBS every 3 days	Pre and 2 hr post meal right from admission	Pre and 2 hr post feeds	6 <sup>th</sup> hourly RBS
<b>Uncontrolled diabetes (FBS &gt; 140, PPBS&gt; 180, HbA1c &gt;8)</b>	Pre and 2 hr post meal right from admission	Pre and 2 hr post meal right from admission	Pre and 2 hr post meal right from admission	Pre and 2 hr post feeds	2- 4 hourly RBS
<b>Dangerously uncontrolled Diabetes (Any RBS value &gt; 400 mg/dl)</b>	<ul style="list-style-type: none"> <li>- Check urine ketones and VBG</li> <li>- Insulin infusion for RBS control</li> <li>- If acidosis / ketosis +, manage DKA as per standard protocol</li> <li>- Refer the ‘section on Insulin infusion’ for detailed description</li> </ul>				

## Part 2: Choice of therapy

### a. Can OHAs be used?

- For patients with Diabetes already on OHA  
OHA can be continued if all the following criteria are met:
  - Patient with normal sensorium and taking oral feeds
  - Blood glucose within target range (pre-meal < 140 mg/dl; post-meal < 180 mg/dl)
  - No / mild COVID symptoms
  - Normal renal and liver function tests
- OHAs to be avoided in COVID infection: SGLT2 inhibitors (risk of dehydration, DKA), Sulfonyl ureas (risk of hypoglycemia)
- OHAs preferred: Metformin , DPP4 inhibitors (Vildagliptin / Teneagliptin / Sitagliptin)
- Newly diagnosed Diabetes patients may be started on OHA provided they meet the foresaid criteria and Pre-meal < 140 – 180 mg/dl and post-meal < 200 – 250 mg/dl and HBA1C < 8%
- OHAs should not be initiated if any of the plasma glucose value > 250 mg/dl / HBA1C > 8%

### b. Insulin

#### Indications

- In all Category C patients
- Patients with renal / liver dysfunction
- Patients receiving steroids
- Patients with no / mild symptoms with pre-meal glucose > 180 mg/l or post-meal glucose > 250 mg/dl / HBA1C > 8 %

#### Choice of Insulin regimen

- Basal-bolus insulin regimen should be used (Patients already on pre-mixed insulin regime should also be changed to basal bolus therapy)
- Basal and bolus insulin should be in the ratio 50: 50
- The concept of sliding scale insulin in patients with oral intake is obsolete and should not be practiced

<b>Patients and glycemic profile</b>	<b>Initial total Daily Dose (units/kg body weight)</b>
<b><u>Known Diabetes mellitus on Insulin + OHAs</u></b> <b>Diabetes on treatment with reasonable control (FBS &lt;140, PPBS &lt; 180 on admission)</b>	- Calculate total number of units of insulin patient has been receiving and change to basal bolus regime (1:1) - Approximate equivalent doses of OHAs and Insulin: 1 mg Glimepride = 5 mg Glibenclamide = 500 mg Metformin = 5 units of Insulin (according to expert opinion)
<b>Diabetes on treatment which is uncontrolled (FBS &gt; 140, PPBS &gt; 180, HbA1c &gt; 8)</b>	- Dosage increased by 25% from the estimated TDD
<b>On oral agents / life style therapy with HBA1C &lt; 7 %</b>	✓ Needs corrective insulin dose only ✓ If blood glucose consistently > 140 mg/dl, add basal insulin at 0.1 U/kg
<b>Use of steroids</b>	
<b>Diabetes with reasonable control (FBS &lt;140, PPBS &lt; 180 on admission)</b>	Dosage increased by 25% from the estimated TDD
<b>Uncontrolled diabetes on admission (FBS &gt; 140, PPBS &gt; 180)</b>	Dosage increased by 50% from the estimated TDD (to be tapered as steroid doses are weaned)
<b>Newly diagnosed Diabetes mellitus</b>	
<b>Age ≥ 70 / eGFR &lt; 60 ml/min/1.73m<sup>2</sup></b>	0.2 – 0.3 U/kg
<b>DM with glucose 140-200 mg/dl or HBA1C 8-9.9%</b>	0.4 U / kg
<b>DM with glucose 200 – 400 mg/dl or A1C ≥ 10%</b>	0.5 U/kg

- **Choice of Basal insulin and dosage**

- NPH given twice daily is the preferred basal insulin in terms of comparable efficacy with newer analogues, easy availability and reduced cost
- Glargine / Detemir may be continued in patients already on the same.
- Starting dose of basal insulin = 0.5 X Total daily dose
- If NPH is used, 2/3rds of calculated dose in the morning and 1.3<sup>rd</sup> at bed time
- Dose increments of basal insulin to be done according to the fasting blood glucose values
  1. Increase by 10 % if FBS 140 – 199 mg/dl

2. Increase by 20 % if FBS 200 – 299 mg/dl
3. Increase by 30 % if FBS 300 – 399 mg/dl

- **Choice of Prandial Insulin and dosage**

- Regular insulin is the first-choice prandial insulin
- Patients already on Lispro / Aspart can continue to take them
- Starting dose = 0.5 X total daily dose divided before each meal
- If patient has reduced oral intake give 50% or less of prandial insulin
- Do not administer prandial insulin if patient is not able to eat

- **Correctional dose of prandial insulin**

Supplemental dose of insulin can be calculated based on the corrective insulin dose formula

Application of corrective Insulin dose formula

- Correction factor = 1700 / Total daily dose of insulin
- Corrective Insulin dose = (Blood glucose – 100) / Correction factor

1) Dosage guide for corrective insulin dosage (in addition to prandial insulin)

Blood glucose (mg/dl)	Usual (units)	Insulin sensitive (Patients not eating / elderly / impaired renal function)	Insulin resistant (TDD > 80 units / corticosteroid use)
>141-180	4	2	6
181 – 220	6	4	8
220 – 260	8	6	10
260 – 300	10	8	12
301 – 350	12	10	14
350 – 400	14	12	16
>400	16	14	18

NB:

- Half of the supplemental dose to be given at night

- If fasting and premeal plasma glucose are persistently above 140 mg/dl in the absence of hypoglycemia, increase scale of insulin from the insulin sensitive to the usual or from the usual to the insulin-resistant column.

- If a patient develops hypoglycemia (<70 mg/dl), decrease prandial insulin from the insulin-resistant to the usual column or from the usual to the insulin-sensitive column

**Calculation of new total daily dosage**

Date	BB	AB	BL	AL	BD	AD
2/11/2020	245	330	210	260	180	260
	R4 N4	R2	R4		R4	N6
3/11/2020	137	160	142	173	132	170
	R6 N4		R4		R5	N5

**A model of glucose monitoring chart for IP patients; R- Regular Insulin, N- NPH Insulin ;**

Correction boluses given before and after the meals should be added to the pre meal bolus on next day.

**Part 3: Use of Insulin infusion**

**Indications**

- Critically ill patient in ICU
- Continuous naso-jejunal feeding
- Total parenteral nutrition
- DKA / HHS
- Peri-operative period
- Labor and delivery

**Infusion protocol**

- Preparation of Insulin infusion: 1-unit insulin in 1 ml 0.9% NaCl
- Flush 50 ml through all IV tubing before infusion begins
- Target blood glucose: 140 – 180 mg/dl
- Threshold for starting infusion: > 180 mg/dl
- If initial Blood glucose 181 – 299 mg/dl → divide by 100 and round off to nearest 0.5 for initial infusion rate (without bolus)
- If initial blood glucose ≥ 300 → divide by 100 and round off to nearest 0.5 for initial drip rate and bolus to be given (eg: If initial blood glucose is 312 mg/dl; 312/100 = 3.12,

rounded off as 3 units/hr. A bolus of 3 units also need to be given – dosage same as that of infusion rate)

- Check blood glucose hourly until stable (3 consecutive values within target range) and every 2 hours afterwards
- Consider hourly glucose monitoring again if there is any change in insulin infusion rate / significant change in clinical condition / initiation or cessation of steroids or vasopressors or renal replacement therapy or TPN, tube feeds

### **Transition from IV to subcutaneous regimen**

- Once critically ill patients become clinically stable and ready for transfer out of the ICU, and are tolerating at least 50% of their diet, or are on a stable regimen of TPN or PPN, they are ready to come off the insulin infusion
- Determine the average hourly rate of insulin over 8 hours (relatively stable rates, no IV dextrose administration)
- Multiply this number by 3 to determine the total IV insulin requirements in past 24 hours (TDD-IV)
- Use 60% to 80% of the total TDD-IV to derive your TDD of SC insulin (TDD-SC).
- If patients were taking nothing by mouth, the TDD-SC number is equivalent to the patients' basal insulin.
- If patients were eating over the past 24 hours, then one-half of the TDD-SC is bolus and the other half basal.
- Overlap IV insulin infusion for a minimum of 4 hours if S/C insulin glargine is given without S/C fast-acting insulin or only 2 hours if S/C fast-acting insulin is given along with glargine



#### Part 4: Optimization of diet and nutrition

	<b>COVID taking food by mouth (with or without steroids)</b>	<b>COVID nasogastric feeds (with or without steroids)</b>
<b>Underweight (BMI &lt; 18.5 kg/m<sup>2</sup>)</b>	Total calorie 30 kcal/kg body weight. Protein: 1 g/ kg	Liquid feeds (1kcal/ml) designed by dietician. Major feeds : Minor feeds calorie ratio 2:1 to 3:2 Major feeds at 7 am, 1 pm and 7 pm Minor feeds at 10 am 4 pm and 10 pm Total calorie 30 kcal/ kg body weight Protein- 1 g/kg
<b>Normal weight (BMI 18.5- 23 kg/m<sup>2</sup>)</b>	Total calorie 25 kcal/kg BW Protein 1 g/ kg	Total calories-25 kcal/kg body weight Protein- 1g/kg as major and minor feeds
<b>Overweight (23-27 kg/m<sup>2</sup>)</b>	Total calorie 20-25 kcal/ kg BW Protein should be 1 g/ kg	Total calories- 20 to 25 kcal/kg body weight Protein- 1g/kg as major and minor feeds
<b>Obese (&gt; 27 kg/m<sup>2</sup>)</b>	Total calorie 20 kcal/kg BW Protein should be 1 g/ kg	Total calories-20 kcal/kg body weight Protein- 1g/kg as major and minor feeds

Ref: ESPEN guidelines for nutritional management in COVID patients

#### Parenteral nutrition

- Parenteral nutrition preferred over enteral nutrition in:
  - ✓ uncontrolled shock and unmet hemodynamic and tissue perfusion goals;
  - ✓ life-threatening hypoxemia, hypercapnia or acidosis.
- 4 grams/kg of dextrose as 25% dextrose neutralised with insulin (6-10 units insulin/25 gram glucose)
- Full TPN should be considered if NPO expected to continue after 48 hours
- Continuous insulin infusion with appropriate monitoring should be instituted

**Part 5: Management of Hypoglycemia**  
**Management of hypoglycemia**

			<b>Treatment</b>
<b>Conscious; on oral feeds</b>	<b>on</b>	BG: 50-69 mg/dl	15-20 gm simple CHO
		BG: < 50 mg/dl	20-30 gm simple CHO
<b>Conscious; but NPO</b>	<b>but</b>	On IV insulin	- Stop IV infusion - Give bolus 25D 50-100 ml - Start 10% D @ 25 ml/hr - Once BG persistently > 100 mg/dl, stop 10% D and restart IV insulin @ 50 % dose
		On S/C insulin	- Give bolus 25D followed by 10%D infusion - Once BG > 100, stop 10D infusion and restart s/c insulin after adjustments
<b>Unconscious</b>		No IV access	Glucagon 1 mg IM Once IV established, do the steps outlined for conscious patients

**Insulin adjustment in hypoglycemia**

- **Fasting hypoglycemia:** Long acting basal insulin reduced by 20% if BG 50-70 mg/dl  
Basal insulin reduced by 30% if BG < 50 mg/dl.  
If patients received corrective insulin before the event, consider increasing sensitivity factor of corrective insulin
- **Postprandial hypoglycemia:** Reduce bolus (nutritional) insulin by 20%–50% for the duration that patients’ oral food intake is below baseline. If patient had received corrective insulin before the event, consider increasing sensitivity factor of corrective insulin

## 18. Vaccine induced thrombosis with thrombocytopenia syndrome (TTS)

### Definition:

TTS is defined by the presence of a thrombosis/thromboembolism, generally in uncommon locations, such as cerebral venous sinus or splanchnic veins and marked thrombocytopenia ( $<50 \times 10^9/L$ ) following vaccination with a COVID-19 nonreplicant adenovirus vector-based vaccine.

Cases of thrombosis/thromboembolism (i.e., pulmonary, deep vein thrombosis, coronary arteries, cerebral arteries) in common location have also been reported following vaccination with a COVID-19 non-replicant adenovirus vector-based vaccine

### Incidence

The cumulative incidence of TTS following vaccination with a non-replicant adenovirus vector-based vaccine ranges from 0.5 to 6.8 cases per 100 000 vaccinees. Incidence rates differ depending on the vaccine, age, sex, geographical distribution and interpretation of the case definition. The observed-to-expected rate is higher following vaccination with the ChAdOx-1 vaccine, in females and in patients aged  $<60$  years. Most TTS cases have been reported within 3 to 30 days following vaccination with a COVID-19 non-replicant adenovirus vector-based vaccine.

### Risk factors

The main risk factors for TTS following vaccination with COVID-19 adenovirus vector-based vaccines are the use of non-replicant adenovirus vector-based vaccines and younger age.

There is currently no evidence that traditional risk factors for thrombosis/thromboembolisms increase the risk of TTS in this context.

### Pathophysiology

TTS has been associated with the presence of anti-platelet factor 4 (anti-PF4) antibodies. There are similarities with autoimmune heparin-induced thrombocytopenia (aHIT). TTS may be caused by the binding of anti-PF4 to platelets, causing platelet activation and aggregation, thrombosis, platelet consumption, and thrombocytopenia. However, the exact mechanisms are still unclear and should be further investigated.

### Clinical presentation

TTS should be suspected in patients presenting with

- severe and unusual headache,
- abdominal pain with or without vomiting,
- sudden onset of breathing difficulty,
- chest pain or limb pains,

particularly in those aged under 60 years, within four weeks following vaccination.

Patients with suggestive clinical symptoms should promptly undergo investigations to rule out thrombotic events and presence of thrombocytopenia.

### **Laboratory diagnosis**

Individuals who present with thrombosis within four weeks following vaccination should be evaluated for

- thrombocytopenia,
- increased D-dimer and
- positive anti-PF4 antibodies.

An enzyme-linked immunosorbent assay (ELISA) should be used to detect anti-PF4 antibodies, as rapid immunoassays are not as sensitive. The presence of antiPF4 antibodies in a patient with a thrombotic event and thrombocytopenia following COVID-19 vaccination is highly suggestive of TTS.

Other biomarkers can be helpful in the laboratory diagnosis of TTS, including D-dimer, fibrinogen, and blood smear to confirm reduced platelets and to rule out platelet clumping.

The case definition implies the absence of a better alternative explanation for the condition.

### **Imaging**

Suitable imaging examinations should be performed in patients with suspected TTS as soon as possible, depending on anatomical location, especially in those who present with thrombocytopenia within 30 days post-vaccination.

**Table 1:** Major and minor criteria for thrombocytopenia, thrombotic events and laboratory examinations.

Classification	Major criteria	Minor criteria
<b>Thrombosis</b>	<p><b>CONFIRMED</b> diagnosis of thrombosis by imaging study, surgical, or pathology findings consistent with thrombosis/thromboembolism in an <b>uncommon location</b>:</p> <ul style="list-style-type: none"> <li>• cerebral veins OR</li> <li>• splanchnic veins OR</li> <li>• multiple organ</li> </ul>	<p><b>CONFIRMED</b> diagnosis of thrombosis by imaging study, surgical, or pathology consistent with thrombosis/thromboembolism in a <b>common location</b>:</p> <ul style="list-style-type: none"> <li>• pulmonary arteries/veins OR</li> <li>• limb veins OR</li> <li>• coronary arteries OR</li> <li>• cerebral arteries OR</li> <li>• other arteries/veins</li> </ul> <p>OR</p> <p><b>SUGGESTIVE</b> thrombosis by supporting imaging or laboratory findings <b>suggestive but not definitive</b> of thrombosis/thromboembolism in any location</p> <p>OR</p> <p><b>SUGGESTIVE</b> thrombosis by specific <b>clinical syndromes</b> consistent with thrombosis or thromboembolism event in any location</p>
<b>Thrombocytopenia</b>	<p>Platelet count: &lt;50 x 10<sup>9</sup>/L AND Confirmatory peripheral smear showing reduced platelets AND No evidence of platelet clumping</p>	<p>Platelet count: &gt; 50 x 10<sup>9</sup>/L - &lt;150 x 10<sup>9</sup>/L</p> <p>OR</p> <p>&gt;50% decrease from baseline platelet count</p>
<b>Laboratory (other than thrombocytopenia)</b>	<p>Positive anti-platelet factor 4 antibodies (with ELISA) or platelet functional assay (i.e., serotonin release assay)</p>	<p>D-dimer &gt; 4000 µg/L fibrinogen equivalent units (FEU)</p>

**Table 2.** WHO classification of TTS following vaccination with a COVID-19 vaccine is based on the degree of certainty.

Classification	Level 1 (Confirmed case)		Level 2 (Probable case)		Level 3 (Possible case)
	Major / Minor	Major	Minor	Major	Minor
Thrombosis	Major / Minor	Major	Minor	Major	Minor
Thrombocytopenia	Major / Minor	Major	Major	Minor	Minor
Laboratory (Other than thrombocytopenia)	Major	Minor	Minor	Minor	Minor / No laboratory

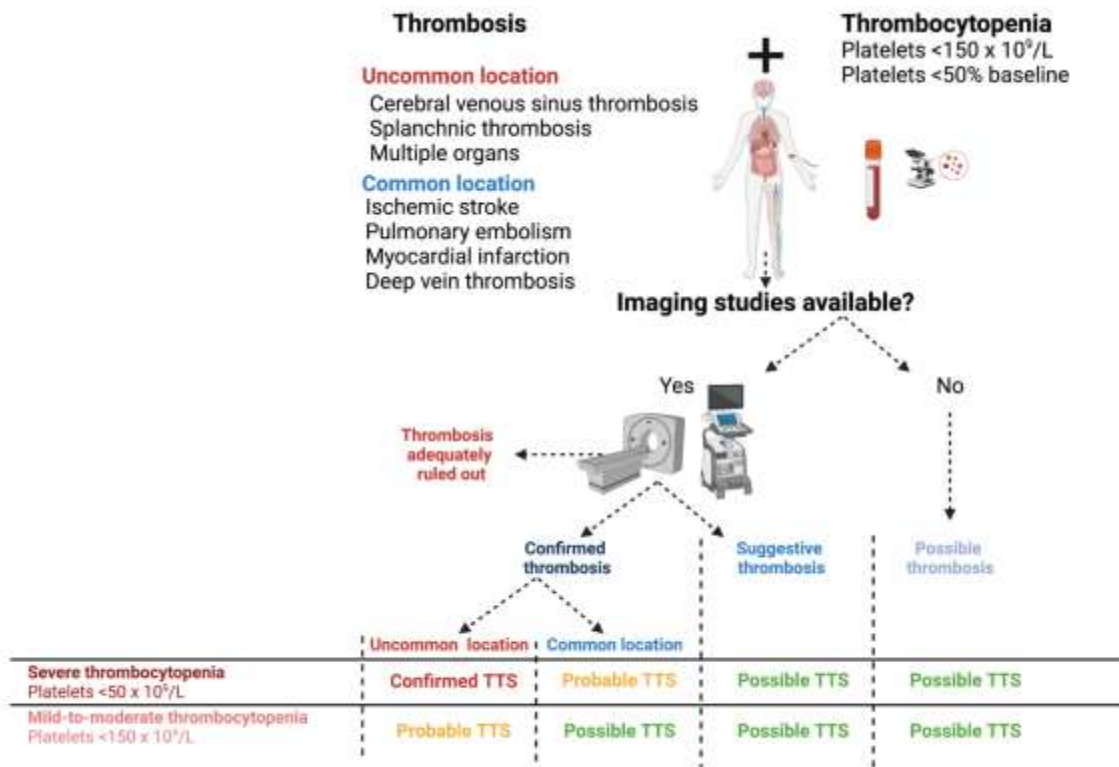
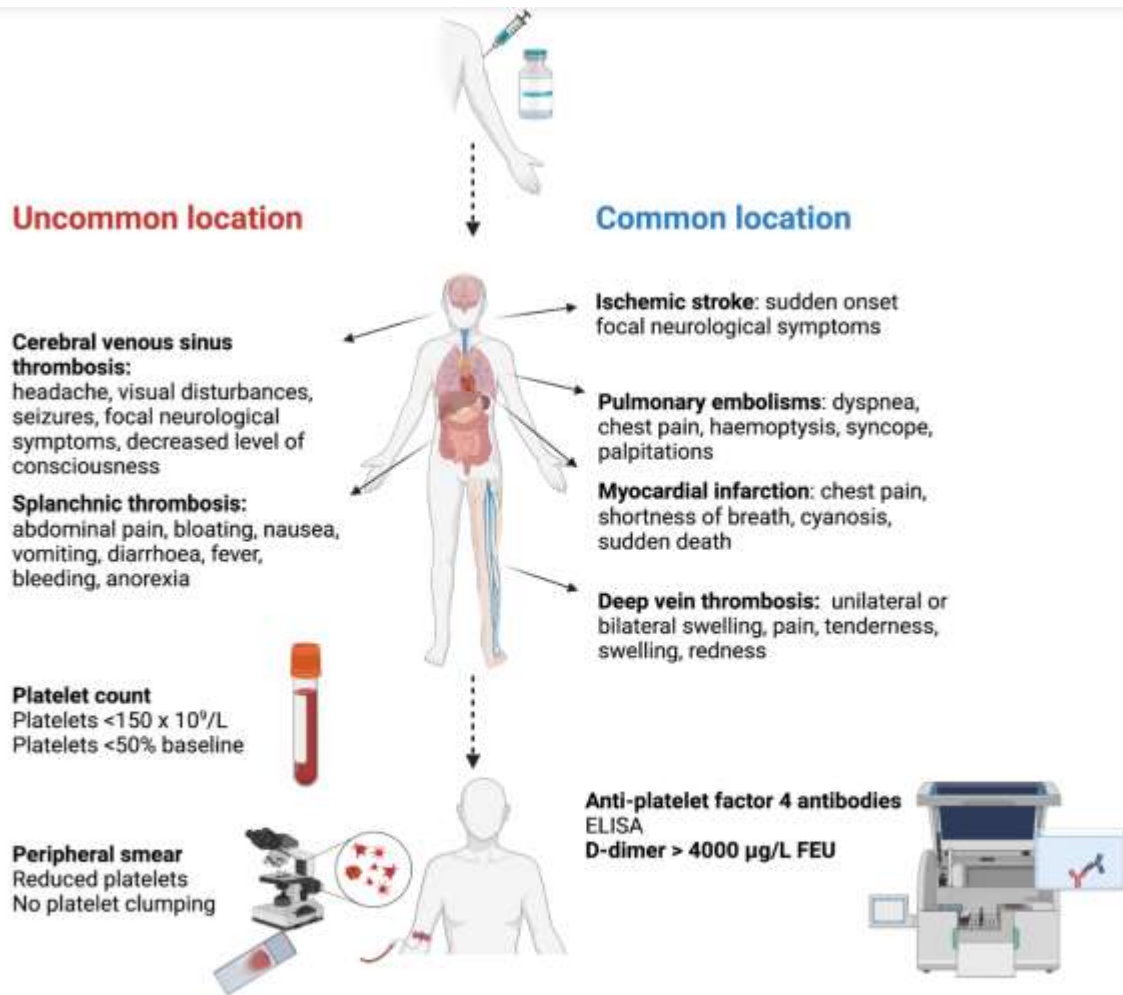


Figure 1: Algorithm for the clinical diagnosis of thrombosis thrombocytopenia syndrome

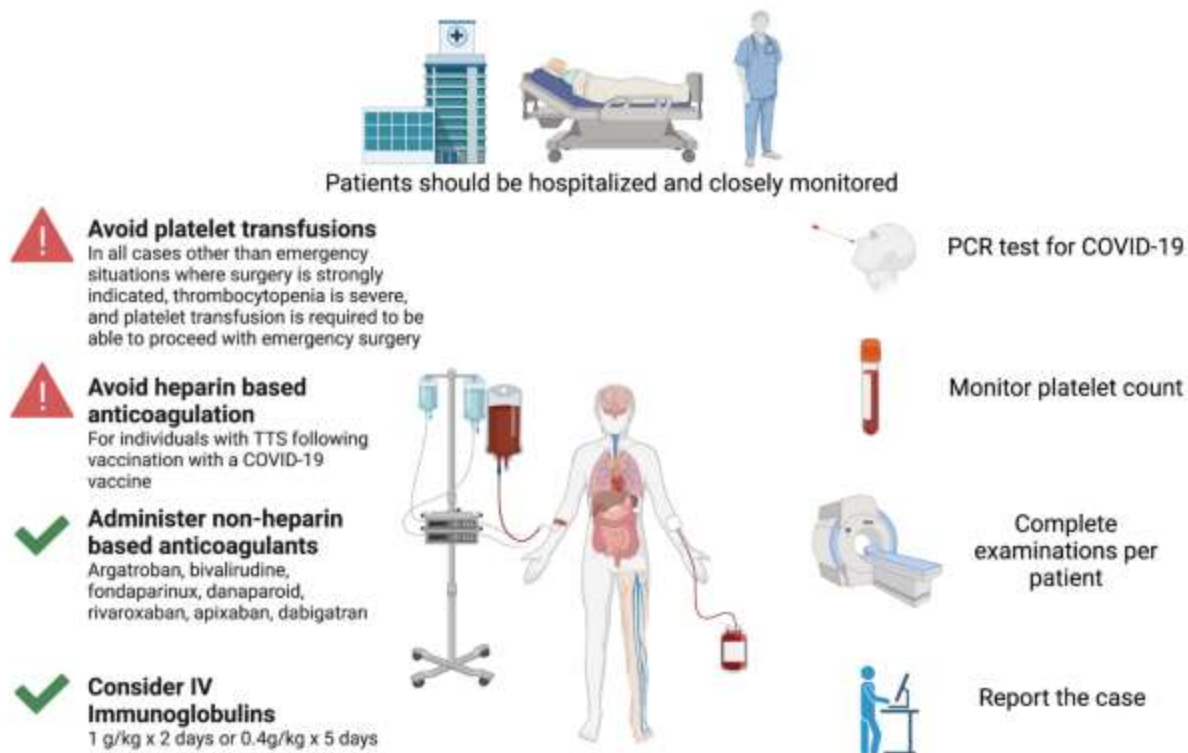
### Clinical case management

Vaccinated individuals should be advised to seek immediate medical attention if they develop symptoms including severe or persistent headache, blurred vision, shortness of breath, chest pain, leg swelling, persistent abdominal pain or unusual skin bruising and/or petechiae (tiny purple, red, or brown spots on the skin) occurring within four weeks after vaccination, although some cases have been reported later than 30 days post-vaccination.

These patients should be investigated for thrombosis and thrombocytopenia. Reporting these symptoms must be made easy for the vaccine recipients, and could include helplines and hospital vaccine centre, online reporting systems.



**Figure 2:** Clinical workup in patients with clinical symptoms and signs suggestive of thrombosis with 30 days of vaccination with a COVID-19 adenovirus vector-based vaccine



**Figure 3:** Clinical management of patients with confirmed, probable or possible vaccine related TTS

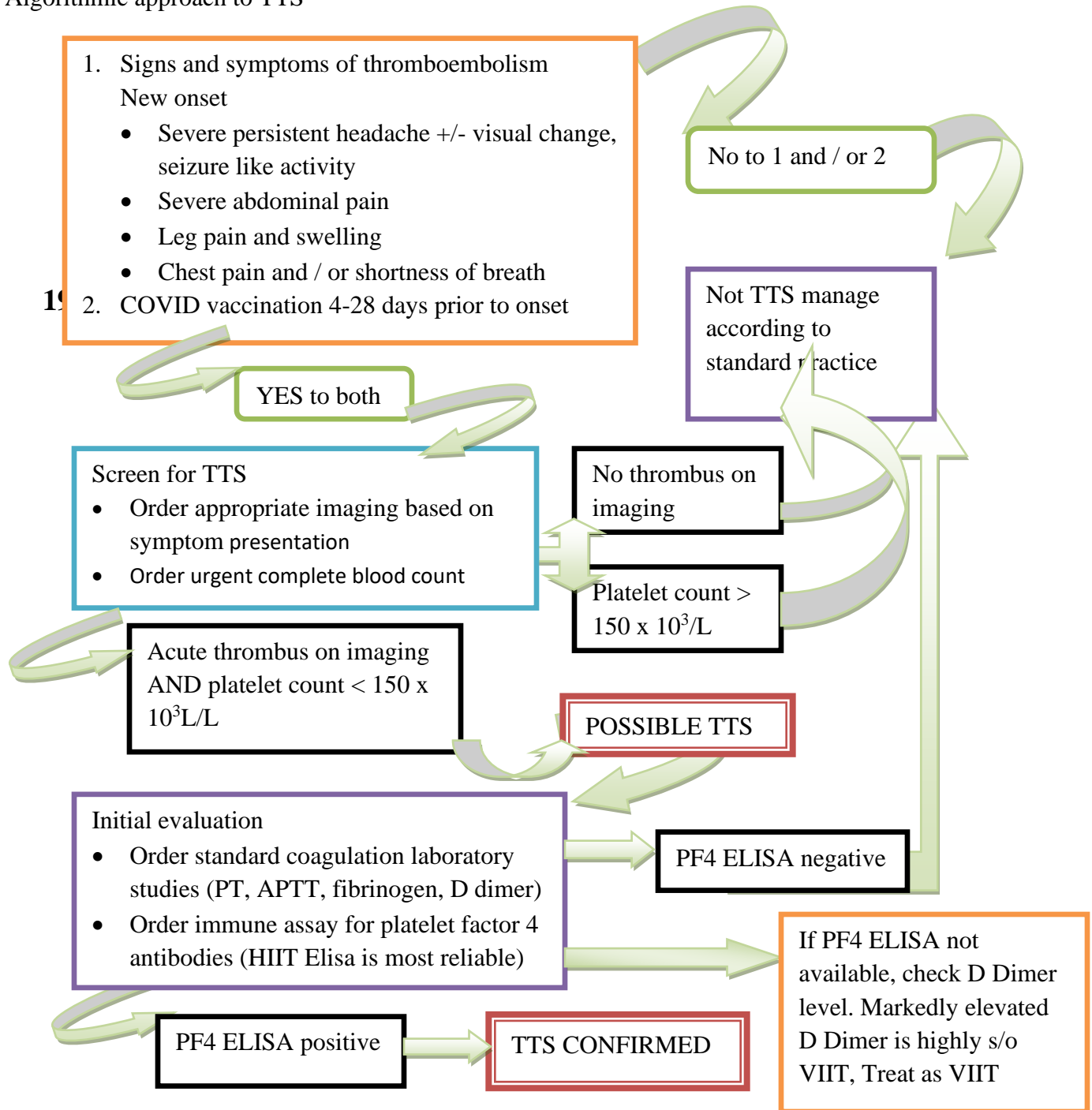
## Treatment

- WHO advises against the use of heparin in individuals with TTS in the context of COVID-19 vaccination (conditional recommendation, very low certainty).
- WHO recommends against the use of platelet infusion for individuals with TTS in the context of COVID-19 vaccination in all cases other than emergency situations where surgery is strongly indicated, thrombocytopenia is severe (platelets  $<50\,000/\mu\text{L}$ ), and platelet transfusion is required to be able to proceed with emergency surgery (strong, very low certainty).
- WHO recommends the use of intravenous immunoglobulins (IVIG) and/or nonheparin-based anticoagulants for individuals with TTS following COVID-19 vaccination (strong, very low certainty).
- WHO does not provide any recommendation for steroid treatment, but notes the general use of steroids and the likelihood that steroids will usually be given in combination with other treatments.

Reference: WHO Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19) Interim guidance 19 July 2021



## Algorithmic approach to TTS



TTS Treatment	
IVIg 1Gg/Kg x 2 days	Give a non heparin anticoagulant fondaparinaux, argatroban, DOAC if platelets > $50 \times 10^3/L$ and no bleeding
Steroids if platelets < $50 \times 10^3/L$	
Avoid platelet transfusion / heparin	

## 19. Other CDSCO EUA approved drugs

### 2-Deoxy-D-Glucose [2 DG]

2-Deoxy-D-Glucose (2-DG) is a synthetic glucose analogue. 2-deoxy-D-glucose (2-DG) has emerged as a polypharmacological agent for COVID-19 treatment due to its effects on the glycolytic pathway, anti-inflammatory action, and interaction with viral proteins. On May 01, 2021, DCGI granted permission for Emergency Use of the drug, 2-Deoxy-D-Glucose as an adjunct therapy in moderate to severe COVID-19 patients for use in hospital or institutional set up only. The drug comes in powder form in sachet, which is taken orally by dissolving it in water. It selectively accumulates in the virus infected cells and prevents virus growth by stopping viral synthesis and energy production.

DRDO and Dr Reddy's have submitted the findings of phase 3 trial to DCGI, but so far not published or as preprint repositories. The Government press release says that the drug was found to be efficacious in the phase 3 trial.

### Prescribing the drug

Obtain written informed consent before administration being approved only for emergency use.

Obtain approval from Institutional Ethics Committee for emergency use.

Clinical information should be captured in prescribed format and must be submitted to the state registry for ongoing assessment of benefit and adverse events.

### Where can this drug be used

Can be used as an adjunct therapy **along with standards of care** in

- 1] 'Moderate'\* [Presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO<sub>2</sub> <94% (range 90-94%) on room air, Respiratory Rate more or equal to 24 per minute] or
- 2] 'severe'\* (Clinical signs of Pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO<sub>2</sub> <90% on room air)

**AND**

The first onset of symptoms/signs suggestive of COVID-19 illness was observed <10 days

**Currently not studied and should not be used in COVID-19 infection in the following patients**

- Not willing to give informed consent
- Patients with previous history of hypersensitivity or a contra-indication to 2-deoxy-D-glucose or the imaging marker Fluorodeoxyglucose (FDG) or allergy to the constituents
- Age  $\leq$  18 years
- Pregnancy, lactating
- Uncontrolled hyperglycemia
- Use of drugs causing prolongation of QT interval [Azithromycin, Hydroxy chloroquine]

**Dose:**

2-DG: 45 mg/kg body weight AM + 45 mg/kg body weight PM for 10 days or until discharge  
Should be taken in a day, with an interval of at least 12 hours between doses, dissolved in 100 ml drinking water. Patients are required to be fasting (with the exception of clear fluids) preferably for at least 3 hours prior to 2-DG administration.

**Special warnings**

Hyperglycemia: Blood glucose levels have been observed to increase while using 2 DG and requires close monitoring especially in a patient with diabetes.

**Caution:**

- **Uncontrolled diabetes and unstable cardiac conditions.**
- **Drugs known to cause QT interval prolongation, including Hydroxychloroquine and Azithromycin should not be co administered**

Monitor closely:

Vitals

CBC

ECG and monitor QT interval

Blood glucose

References:

1. Verma A, Adhikary A, Woloschak G, Dwarakanath BS, Papineni RVL. A combinatorial approach of a polypharmacological adjuvant 2-deoxy-D-glucose with low dose radiation therapy

to quell the cytokine storm in COVID-19 management. Int J Radiat Biol. 2020 Nov;96(11):1323-1328. doi: 10.1080/09553002.2020.1818865. Epub 2020 Oct 6. PMID: 32910699.

2. CDSCO Permission letter dated 1/5/21

Suggested the use of:

1. Written informed consent in Malayalam
2. Clinical data form
3. The 10-point ordinal scale used in the WHO SOLIDARITY trial for assessment of patient's clinical status