



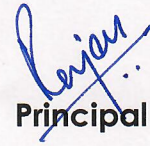
COVID-19 (nCorona) Virus Outbreak Control and Prevention State Cell
Health & Family Welfare Department
Government of Kerala

COVID 19 TREATMENT GUIDELINES FOR KERALA STATE

No.17/31/F2/ 2020 HEALTH- 25th April 2021

In superseding all the previous advisories, guidelines regarding the patient management and treatment, the revised updated Treatment Guidelines Version 3 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.


Principal Secretary

COVID-19: Treatment Guidelines for Kerala state

**Version 3,
25th April 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 ,SOLIDARITY, 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.

This document has been developed as a clinical guideline to streamline the treatment of SARS-CoV 2 infection based on the available evidence from across the world and also based on data 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.

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

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

*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>Adult: dyspnea and/ or hypoxia, fever, cough, SpO₂ ≤ 94% (range 90-94%) on room air, Respiratory Rate ≥ 24 per minute.</p> <p>Child – dyspnea and or hypoxia, fever, cough, including SpO₂ ≤ 94% (range 90-94%) on room air, Respiratory Rate ≥ 24 per minute. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40</p>	C
Severe	<p>Adult: Pneumonia plus one of</p> <ul style="list-style-type: none"> ▶ respiratory rate ≥ 30 breaths/min ▶ severe respiratory distress ▶ SpO₂ ≤ 90% on room air. <p>Child: cough/dyspnoea, plus one of</p> <ul style="list-style-type: none"> ▶ central cyanosis or SpO₂ ≤ 90%; ▶ severe respiratory distress (e.g. grunting, chest in-drawing); ▶ signs of pneumonia with danger signs: (inability to breastfeed or drink, lethargy, unconsciousness, or convulsions). ▶ Other signs of pneumonia like chest in drawing, fast breathing (in breaths/min): < 2 months ≥ 60; 2–11 months ≥ 50; 1–5 years ≥ 40. 	C

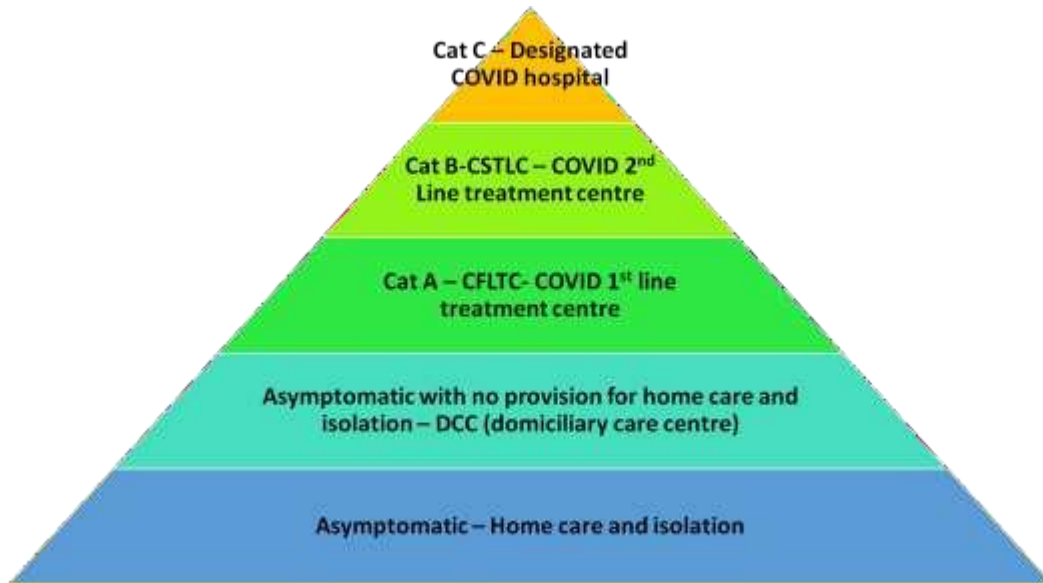
Severity categories for treatment purpose

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

4. Treatment

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 >7.6%	Hypoxia – SpO2 ≤ 94 % on room air	CRP > 100 mg /L
Hypertension	Tachycardia PR > 125/min	CPK > twice upper limit of normal
Cardiovascular disease	Respiratory distress RR > 24/min	Ferritin > 300mcg/L
Preexisting pulmonary disease	Hypotension BP < 90systolic, 60mm Hg Diastolic	LDH > 245 U /L
CKD	Altered sensorium	TROP T elevation
CLD	PAO2/FiO2 < 300 mm of Hg	D Dimer > 1000ng/ml
On immunosuppressives/biologicals		
HIV CD4 <200 / congenital immunodeficiency disorders		Multi organ dysfunction
Age > 65 yrs		*ALC < 0.8
BMI >30		#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 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 negatives cases with high clinical index of suspicion of COVID – 19.

Imaging classification	Rationale	CT appearance
Typical appearance	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
Indeterminate appearance	Non specific imaging features of COVID 19 pneumonia	Absence of typical features AND Presence of 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
Atypical Features	Uncommonly or not reported features of COVID-19 pneumonia	Absence of typical features or indeterminate features AND Presence of Isolated lobar or segmental consolidation without GGO Discrete small nodules (centrilobar, tree in bud) Lung cavitation Smooth interlobular septal thickening with pleural effusion
Negative for pneumonia	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>

Typical Features for Pulmonary Involvement of COVID-19
Obligatory Features
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
Confirmatory Patterns
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

Overview of CO-RADS Categories and the Corresponding Level of Suspicion for Pulmonary Involvement in COVID-19		
CO-RADS Category	Level of Suspicion for Pulmonary Involvement of COVID-19	Summary
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
<p>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.</p>		

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

CT Score	Severity
<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 pulmonary mucormycosis.

Treatment strategies according to clinical categorization and Risk stratification

Category	Treatment	Precautions
A	Symptomatic treatment	Categorization should be reassessed every 28-48 hours for Category A.
B	<p>Tab Ivermectin 200mcg/kg/day (not exceeding 12mg) once a day for 3-5 days only for those with high risk factors</p> <p>Inhalational budesonide 800mcg twice a day for 5 to 7 days if fever and cough are persistent beyond five days of disease onset</p>	<p>Ivermectin use is based on low certainty evidence and is recommended by AIIMS-ICMR national task force COVID 19 guidelines. NIH guidelines for COVID 19 specify that there is no evidence for or against COVID 19</p> <p>Given via MDI/DPI [metered dose inhaler/dry powder inhaler]</p>
C	<p>Tab Favipiravir 1800mg BD x 1 day then 800mg BD x 6 days</p> <p>OR</p> <p>Tab Ivermectin 200mcg/kg/day (not exceeding 12mg) once a day for 3-5 days</p> <p>PLUS</p> <p>Inhalational budesonide 800mcg twice a day for 5 to 7 days if fever and cough are persistent beyond five days of disease onset</p>	
C – moderate severity (Resp rate between 24-29, SpO2 between 91-94 on	<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>*if remdesivir is not available or</p>	Remdesivir [EUA] based on limited available evidence and only in specific circumstances.

<p>room air)</p>	<p>contraindicated treat as Category C</p> <p style="text-align: center;">PLUS</p> <p>Inj Methyl prednisolone 0.5-1 mg/kg/day for 5-10 days</p> <p>Or</p> <p>Inj Dexamethasone – 0.1-0.2 mg/kg/day for 5-10 days</p> <p>PLUS</p> <p>Anti coagulation as per state protocol</p> <p>*Convalescent plasma therapy as per state protocol</p>	<p>If there is no clinical response to the dose of steroid used, as per pulmonologist/Physician directive dose of steroids can be escalated. Duration of steroids should be individualized based on clinical response</p>
<p>C – severe signs and symptoms</p> <p>Resp Rate \geq 30, SpO₂ < 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>*if remdesivir is not available or contraindicated treat as Category C</p> <p style="text-align: center;">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 style="text-align: center;">PLUS</p> <p>Anticoagulation as per state protocol</p> <p>Inj Tocilizumab as indicated below</p> <p>*Convalescent plasma as per state protocol</p>	<p>Remdesivir is contraindicated in</p> <ul style="list-style-type: none"> • AST/ALT > 5 times Upper limit of normal (ULN)[AST/ALT has to be monitored daily] • Severe renal impairment (i.e., eGFR < 30ml/min/m² or need for hemodialysis) • Pregnancy or lactating females
<p>Favipiravir can lead to teratogenicity, transaminitis, neutropenia and dose dependent</p>		

hyperuricemia. Prior to using favipiravir or remdesivir, pregnancy has to be ruled out in all females in reproductive age group. Favipiravir should not be used in pregnant and lactating females. Favipiravir should be stopped if SGPT >5 times upper limit of normal or if creatinine clearance is <30ml/min/m² or if there is doubling of creatinine from baseline without an alternative explanation.

REMDESIVIR

- Only in category C – moderate and severe disease
- No renal or hepatic dysfunction(egfr < 30ml/min/m², AST/ALT > 5 times ULN) – NOT an absolute contraindication

TOCILIZUMAB

Tocilizumab in combination with steroids is now recommended in patients with

1. Recently hospitalized patients who have been admitted to ICU within the prior 24 hours and who require invasive mechanical ventilation, NIV or HFNC [>0.4 FiO₂/30L/min of oxygen flow]

OR

2. Recently hospitalized patients with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation [CRP >75 mg/L was cut off in RECOVERY trial]

IVERMECTIN

- Pregnancy Category C – better to avoid
- Excreted in low concentration in human milk
- Metabolized in liver by Cytochrome p450 isoenzyme 3A4
- Azithromycin co administration may increase serum level of Ivermectin
- Concomittent alcohol use can increase severity of adverse effects

Kerala State COVID 19 guidelines Version 3 April 24, 2021

Treatment guidelines for COVID 19 patients		
Category A		
Symptomatic treatment Reassessment every 24-48 hours for change in category Monitor for dyspnoea, hypoxia (SpO2<94%), high grade fever, severe cough, altered sensorium and excessive fatigability		
Category B		
Tab Ivermectin 200mcg/kg/day (not exceeding 12mg) once a day for 3-5 days if #risk factors present PLUS MDI/DPI Budesonide 800mcg twice a day if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset		
Category C		
Tab Favipiravir 1800mg BD x 1 day then 800mg BD x total 7days OR Tab Ivermectin 200mcg/kg/day (not exceeding 12mg) once a day for 3-5 days PLUS MDI/DPI Budesonide 800mcg twice a day if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset		
Moderate severity (respiratory rate 24-29/min, SpO2 91-94 on room air) Inj Methyl prednisolone 0.5-1 mg/kg/day for 5-10 days Or Inj Dexamethasone – 0.1-0.2 mg/kg/day for 5-10 days PLUS Anti coagulation as per state protocol *see EUA below	Severe (respiratory rate ≥30/min, SpO2 < 90 on room air) Inj Methyl prednisolone 1-2 mg/kg/day for 5-10 days Or Inj Dexamethasone – 0.2-0.4 mg/kg/day for 5-10 days PLUS Anticoagulation as per state protocol *See EUA below	
*EUA/Off label use based on limited available evidence and ONLY in special circumstances		
REMEDSIVIR <ul style="list-style-type: none"> Only in category C – moderate and severe disease (ie requiring supplemental oxygen) AND Within 10 days of symptom onset No renal or hepatic dysfunction(egfr < 30ml/min/m², AST/ALT > 5 times ULN) –NOT an absolute contraindication Recommended dose is 200 mg IV on day 1 followed by 100 mg IV daily for next 4 days 		
TOCILIZUMAB When all below categories are met <ul style="list-style-type: none"> 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 4-6ml/kg (usually a dose of 400mg in a 60Kg adult) in 100ml NS over 1 hour (Single Dose) 		
CONVALESCENT PLASMA <ul style="list-style-type: none"> Early MODERATE disease preferably within 7 days of disease onset Availability of high titre donor plasma (Signal to cut off ratio S/O ≥ 3.5 or equivalent based on the test used) Usual dose is 200ml given over a period of 2 or more hours 		
IVERMECTIN <ul style="list-style-type: none"> To give in high risk Age > 60yrs Cardiovascular disease including HTN, CAD Chronic lung/liver/kidney disease Cerebrovascular disease Obesity <ul style="list-style-type: none"> Pregnancy Category C – better to avoid Excreted in low concentration in human milk Metabolized in liver by Cytochrome p450 isoenzyme 3A4 Azithromycin co administration may increase serum level of Ivermectin Concomittent alcohol use can increase severity of adverse effects 		
FAVIPIRAVIR can lead to teratogenicity, transaminitis, neutropenia and dose dependent hyperuricemia. Prior to using favipiravir or remdesivir, pregnancy has to be ruled out in all females in reproductive age group. Favipiravir should not be used in pregnant and lactating females. Favipiravir should be stopped if SGPT >5 times upper limit of normal or if creatinine clearance is <30ml/min/m ² or if there is doubling of creatinine from baseline without an alternative explanation.		
IVERMECTIN and FAVIPIRAVIR are NOT recommended in children.		
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"> Lung/ heart / liver/ kidney / neurological disease/ Hypertension/haematological disorders/ uncontrolled diabetes/ cancer /HIV- AIDS On long term steroids Pregnant lady Age –more than 60 years. 	Breathlessness, chest pain, drowsiness, fall in blood pressure, haemoptysis, cyanosis [red flag signs] Children with ILI (influenza like illness) with red flag signs (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.	Ivermectin and favipiravir are contra indicated in pregnancy
2.	For moderate and severe SARS Cov 2 bronchopneumonia, Inj remdesivir may be considered on a compassionate basis after obtaining informed consent
3.	For moderate and severe SARS Co V 2 bronchopneumonia, corticosteroids are indicated for 10 days or upto discharge whichever is sooner
4.	The selection of steroids depends on the stage of gestation
5.	If steroids are not indicated for fetal lung maturity, Inj Methylprednisolone 40mg IV OD (ie 0.5-1mg/kg) IV OD, oral prednisolone once a day or IV hydrocortisone 80mg twice a day for 10 days or until discharge whichever is earlier
6.	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 once a day or IV hydrocortisone 80mg twice a day for 10 days or until discharge whichever is earlier
7.	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.
8.	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

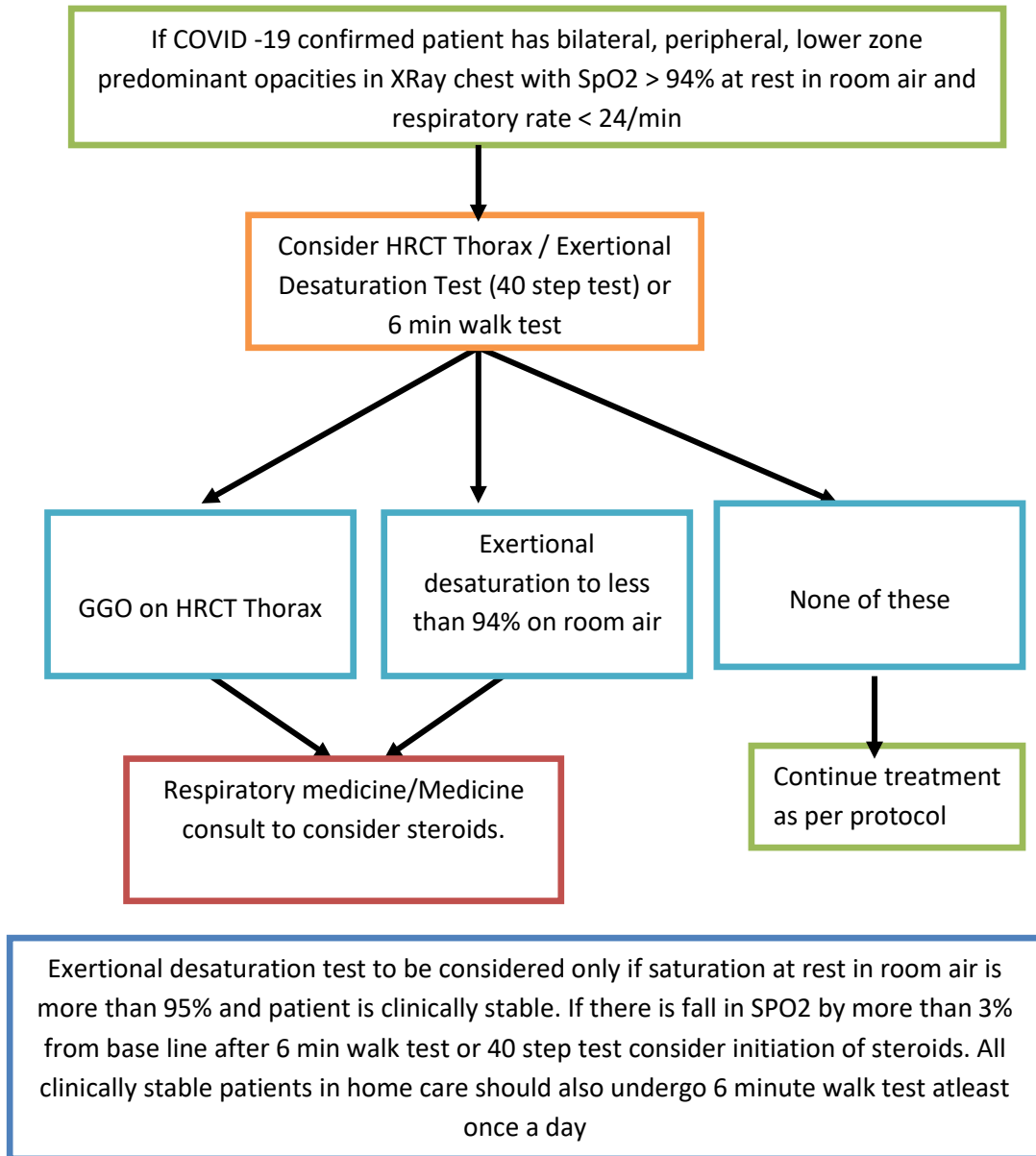
D Dimer cut offs in normal pregnancy

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

Criteria for using Tocilizumab

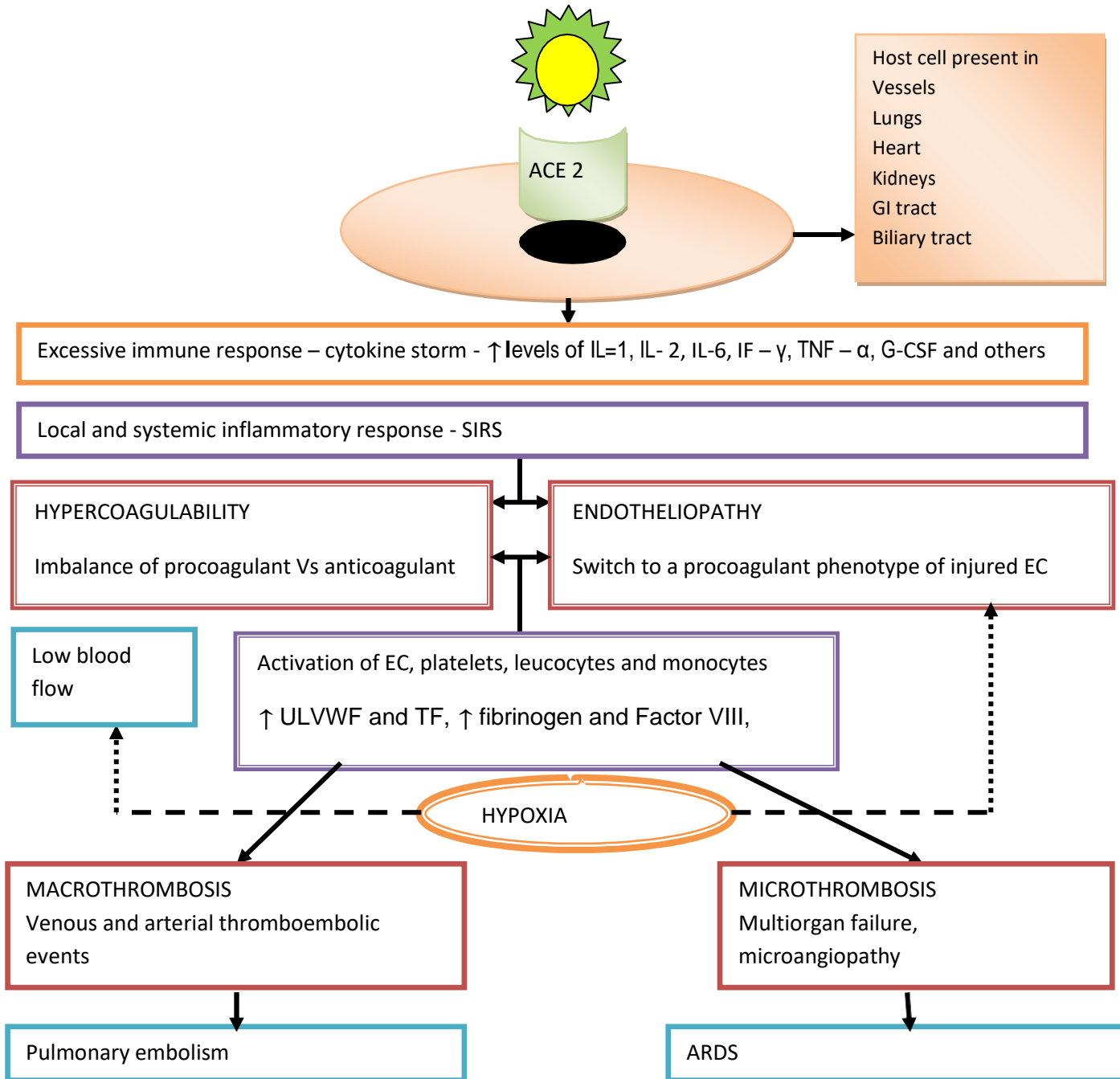
Criteria for using Tocilizumab	Tocilizumab Regimen
<p>Change in recommendation after publication of REMAP-CAP and RECOVERY trial results</p> <p>Tocilizumab in combination with steroids is now recommended in patients with</p> <p>1. Recently hospitalized patients who have been admitted to ICU within the prior 24 hours and who require invasive mechanical ventilation, NIV or HFNC [>0.4 FiO₂/30L/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 >75 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><u>Toxicities/Monitoring Parameters</u></p> <ul style="list-style-type: none"> - Infusion related/ injection site reaction - Monitor LFTs (life threatening hepatotoxicity can occur) - Monitor neutrophils/platelets <p><u>Cautions</u></p> <ul style="list-style-type: none"> - 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. - ALT/AST 3xULN - Neutropenia (ANC < 0.5 K/CUMM) - Thrombocytopenia (< 50 K/CUMM) - Latent or active pulmonary tuberculosis - Active bacterial or fungal infection

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



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

All admitted patients with COVID:

- All admitted patients should be assessed for VTE risk factors, signs or symptoms of DVT and PE, and bleeding risk.

- Increased risk for bleeding includes active bleeding, PLT <50,000/mm³ or INR > 1.8.

- All patients should receive VTE prophylaxis as follows, unless they have a contraindication to anticoagulation:

- o **BMI <40**

- **CrCl >30:** Enoxaparin 30 mg SQ Q12H

- **CrCl ≤30:** Enoxaparin 30 mg SQ daily; Alternative - heparin 5,000 units SQ Q8hrs

- o **BMI ≥40**

- **CrCl >30:** Enoxaparin 40 mg SQ Q12H

- **CrCl ≤30:** Enoxaparin 40 mg SQ daily; Alternative - heparin 7,500 units SQ Q8hrs

- o 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).

Confirmed VTE, based on positive diagnostic test (e.g., LE ultrasound, CTA) or high clinical suspicion in patients who cannot undergo diagnostic testing due to clinical instability.

- Treatment dose anticoagulation – Treat as per standard treatment for acute VTE.

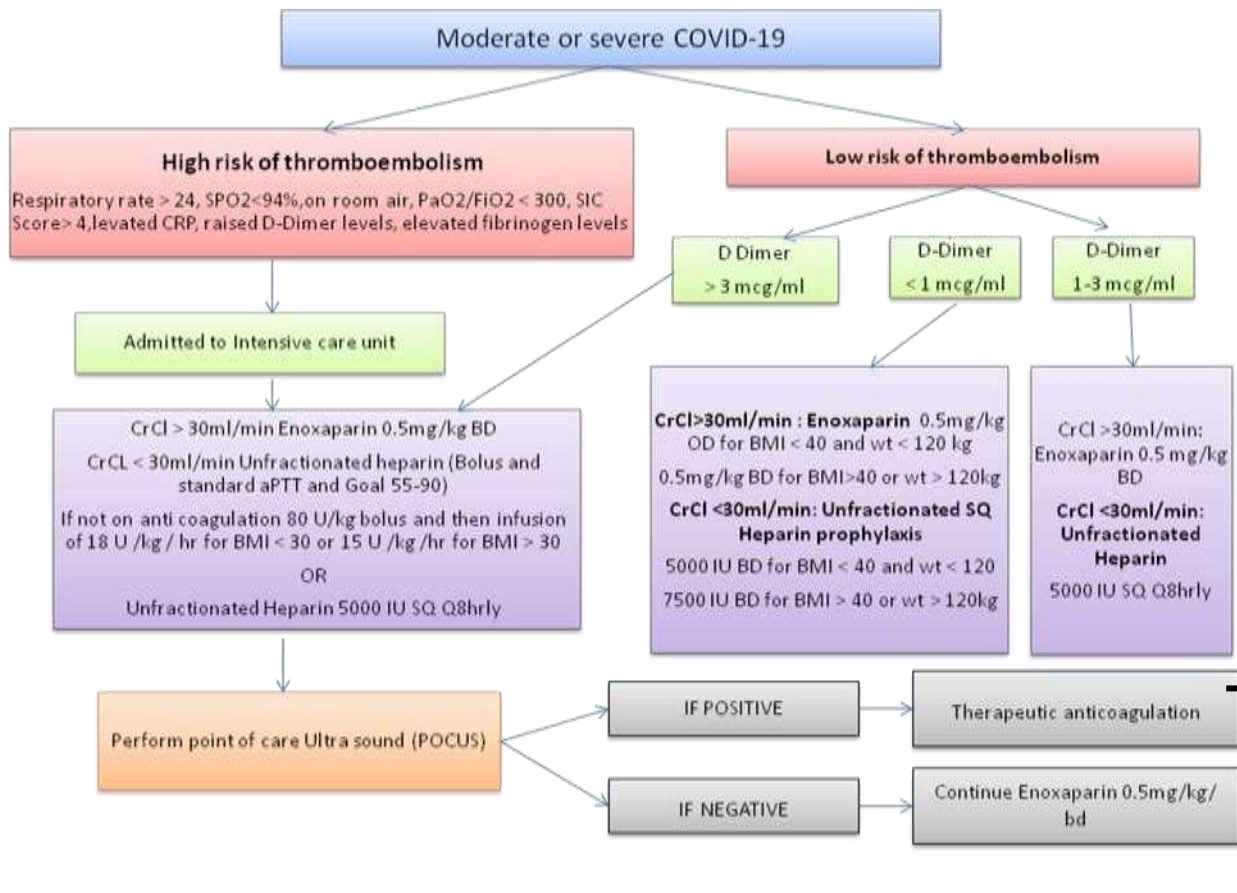
- o Can initiate treatment-dose apixaban or rivaroxaban to avoid need to transition from LMWH to oral agent.

- Apixaban dose: 10mg PO BID for 7 days then 5mg PO BID.
- Rivaroxaban dose: 15mg PO BID for 21 days then 20mg daily.

o CrCl <30 including RRT

- No adjustment for apixaban is needed
 - Avoid rivaroxaban if CrCl<30
 - IV heparin and warfarin is a reasonable alternative to use of apixaban.
- Duration – Minimum of 3 months. Total duration should be determined based on an individualized assessment of the patient’s risk of recurrent VTE and bleeding.

Kerala State Anticoagulation algorithm in COVID -19



Moderate illness: individuals who have evidence of lower respiratory illness by clinical assessment or imaging and a saturation of oxygen (SpO2 ≤ 94%) on room air at sea level

Serious illness: Individuals who have respiratory frequency >30 breaths/min, SpO2 ≤90% on room air at sea level, PaO2/FiO2 < 300 or lung infiltrates > 50%

For COVID positive on Therapeutic anticoagulation during hospitalization, Tab Apixaban 5mg BD to be continued for minimum of 2 weeks after discharge. To reduce dose to 2.5mg BD if Age > 80years or weight ≤ 60kg

SIC score				
Category	Parameter	0 point	1 point	2 points
Prothrombin time	PT-INR	≤1.2	>1.2	>1.4
Coagulation	Total Platelet Count (x 10 ⁹ /ml)	≥150	<150	<100
Total SOFA	SOFA four items	0	1	≥2

Hold anticoagulation if platelet count < 25,000/ml or evidence of current or recent bleeding

If taking anticoagulation at home for any previous indication, may switch to enoxaparin or heparin as per algorithm for the duration of hospitalization unless contraindicated

Post Discharge thrombophylaxis

Should be restricted to patients with COVID -19 patients

1. Modified International Medical prevention registry on Venous Thromboembolism (Improve) VTE risk ≥ 4 ; or
2. Modified IMPROVE VTE risk score ≥ 2 and D-Dimer level ≥ 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 at least 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 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 ≥ 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 Corona 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

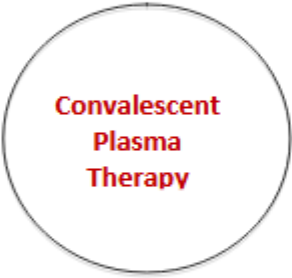
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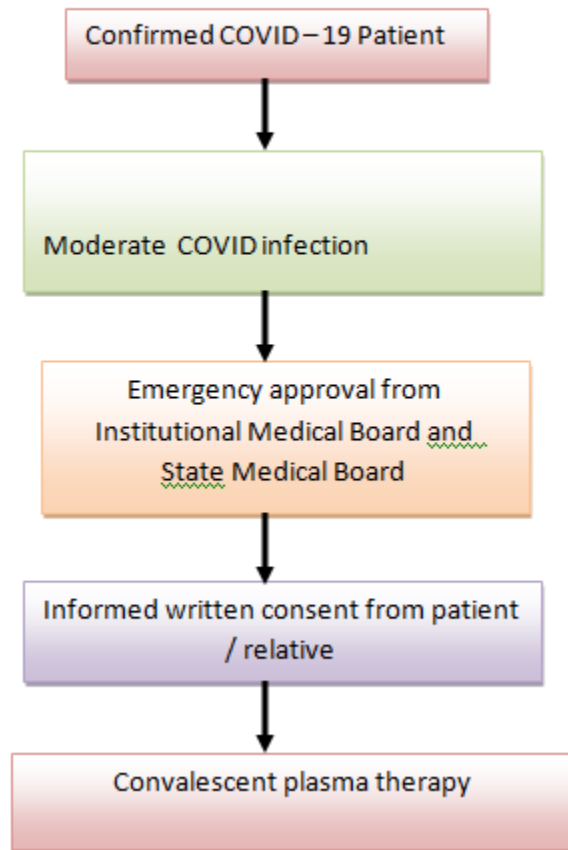
6. ADVISORY TO OPTIMIZE THE EVIDENCE BASED USE OF CONVALESCENT PLASMA THERAPY [CPT] IN COVID 19

- Benefits of CPT in improving the clinical outcomes, reducing severity of disease, duration of hospitalization and mortality in COVID-19 patients are dependent on the concentration of specific antibodies in convalescent plasma that could neutralize the effects of SARS-CoV-2.
- It is speculated that convalescent plasma having low concentration of specific antibody against SARS-CoV-2 may be less beneficial for treating COVID-19 patients as compared to plasma with high concentration of such antibodies. This advisory therefore embraces the principle that a potential donor for convalescent plasma should have sufficient concentration of antibody working against COVID19 as narrated in the matrix below. It also highlights that presence of antibody against COVID-19 in a potential recipient makes transfusing convalescent plasma a futile intervention.
- The Convalescent-plasma-for-COVID (ConCOVID) study was a randomized trial comparing convalescent plasma with standard of care therapy in patients hospitalized for COVID-19 in the Netherlands. The major observation made in this study was that most of the COVID-19 patients already have high neutralizing antibody titers at hospital admission. The same observation was made in the PLACID trial conducted by ICMR.
- Screening for antibodies and prioritizing convalescent plasma to risk groups with recent symptom onset will be key to identify patients that may benefit from convalescent plasma. Ideally convalescent plasma should be administered in those patients with moderate disease severity who present within 3 to 7 days of symptom onset not later than 10 days.
- CPT therefore should only be used, for management of COVID-19 when specific criteria as mentioned in the **DECISION MATRIX** are met.

Box 1: Decision Matrix

Potential donor		Potential recipient
Who can donate <ul style="list-style-type: none"> - Men - Women who have never been pregnant 	 <p>Convalescent Plasma Therapy</p>	In early stage of COVID-19 disease
Appropriate Age 18-65 year		3-7 days from onset of symptoms, but not later than 10 days
Appropriate Body Weight >50 kg		No IgG antibody against COVID-19 by appropriate test
Diagnosis COVID-19 RT-PCR positive		Informed Consent
Physical Status After 14 days of symptom resolution ⁷ (testing negative for COVID-19 is not necessary)		
Screening to rule out ABO incompatibility & blood borne pathogens⁸ such as <ul style="list-style-type: none"> - HIV - HBV - HCV etc. 		
Required Concentration <ul style="list-style-type: none"> - IgG antibody against COVID-19 Titre of 1:640 (ELISA) OR - 13 AU (Absorbance Unit)/mL⁹ (CLIA) OR - Neutralising Antibody Titres of 1:80 (PRNT/MNT) 		

SOP for convalescent plasma administration under compassionate grounds



CONVALESCENT PLASMA (OFF LABEL) may be considered when the following criteria are met

- Early moderate disease preferably within 7 days of symptom onset)
- Availability of high titre donor plasma (Signal to cut off ratio (S/O) ≥ 3.5 or equivalent depending on the kit being used)
- Usual dose is 200ml given over a period of 2 or more hours

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1. Evidence Based Advisory to address Inappropriate Use of Convalescent Plasma in COVID-19 Patients ICMR ADVISORY 17/11/2020

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3. USFDA. Investigational COVID-19 Convalescent Plasma: Guidance for Industry [Internet] 2020 [Accessed on 17thNov, 2020]. Available from:<https://www.fda.gov/media/13678/download>.
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7. 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).¹ 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.²

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 coadministered 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 <30ml/min/m²

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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8. 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.

Rationale for use of Tocilizumab in COVID-19

Pro-inflammatory cytokine levels are elevated in COVID-19 infection. Predictors of mortality from a retrospective, multicentre 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^{1,2}.

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 CRS³.

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 mg⁴.

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

.Guidelines and recommendations:

1) Recommendations for COVID-19 clinical management, National Institute for the Infectious Diseases, Italy:

Tocilizumab: 8 mg/kg (maximum 800 mg/dose), single dose intravenously (1-hour infusion); in absence or with poor clinical improvement a second dose should be administered after 8-12 hours.

Tocilizumab administration should be guided by the presence of 1 or more of following selection criteria: a) PaO₂/FiO₂ ratio < 300, b)rapid worsening of respiratory gas exchange with or without availability of non-invasive or invasive ventilation c)IL-6 levels >40 pg/ml (if not available, see D-dimer levels >1000 ng/ml.)

Therapeutic schedule: 2 administrations (each 8 mg/kg, maximum 800 mg). Second administration to be started at 8-12 hours from the first one. Repeat PCR and D-dimer (+/-IL-6) after 24 hours from each administration.

2) Massachusetts General Hospital COVID-19 Treatment Guidance:

To be given after establishment of clinical status

Grade 1 – mild reaction
Grade 2 – moderate reaction, fever, need for IVF (not hypotension), mild oxygen requirement
Grade 3 – severe, liver test dysfunction, kidney injury, IVF for resuscitation, low dose vasopressor, supplemental oxygen (high flow, BiPAP, CPAP)
Grade 4 – life threatening, mechanical ventilation, high dose vasopressors

Treatment interventions based on grades:

Grade 1 – no treatment
Grade 2 – send for serum IL-6
Grade 3 – send for serum IL-6; consider Tocilizumab, if no effect can repeat x 2 more doses Q8H apart; if no response, consider low dose corticosteroids
Grade 4 – send for serum IL-6; consider Tocilizumab as Grade 3; consider corticosteroids

References:

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9. 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, SpO_2 , Work of breathing
- b. 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 CO₂ 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 CO₂ 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. PaO₂/FiO₂ at 200-300

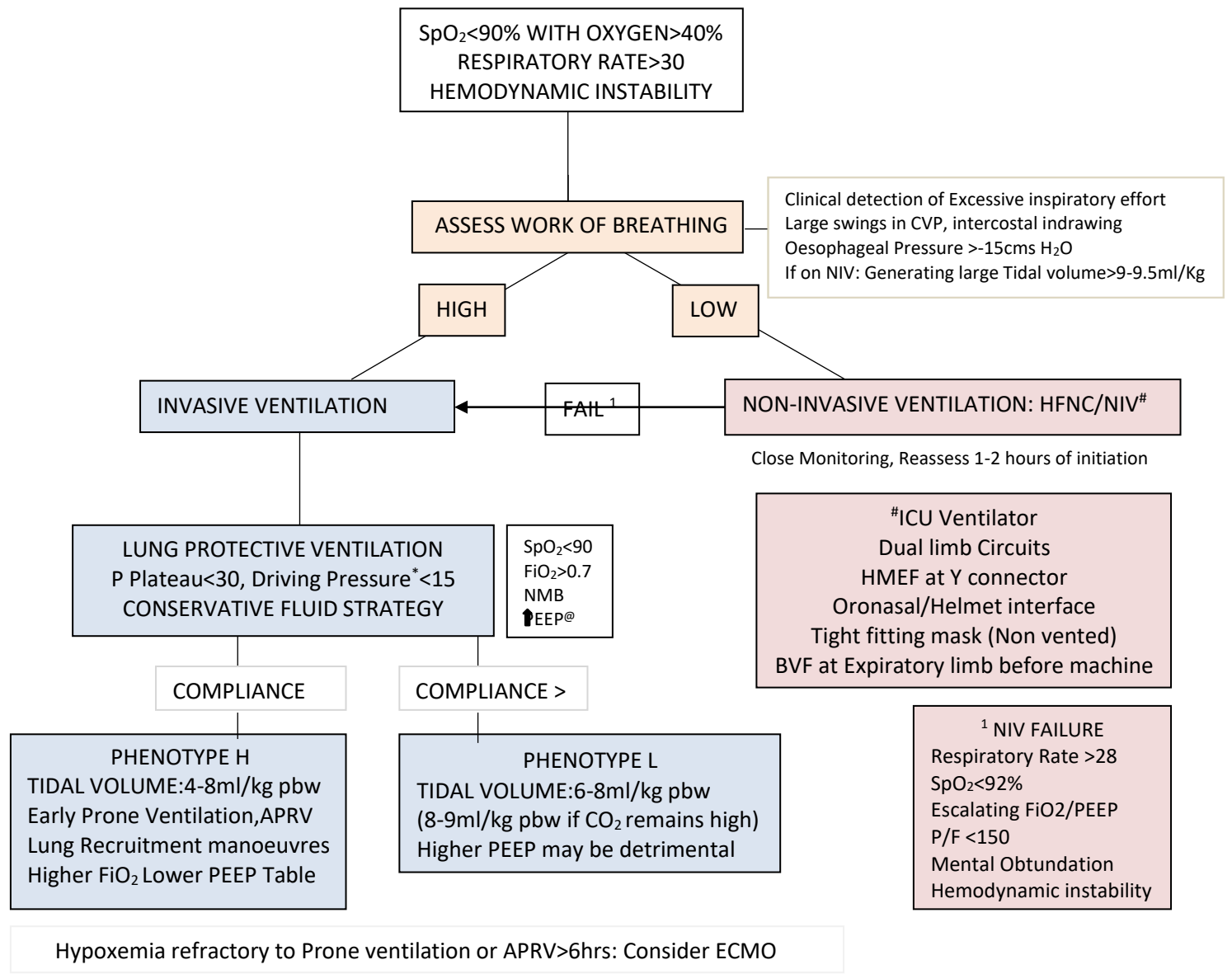
1. Nasal cannula /oxygen mask. Assess if respiratory disease/hypoxemia has remitted. If no improvement in 1-2 hours—go to next step/invasive mechanical ventilation
2. High flow nasal cannula HFNC: **limited recommendation**. If used patient ideally in Negative pressure room or single isolation room with good ventilation. More aerosol formation. Maximum for 2 hours. Close observation is needed. If no improvement /response (Respiratory Rate >35/min SpO₂<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 FiO₂.

ii. PaO₂/FiO₂ 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 SpO₂<93%, accessory muscle use, generating large tidal volume>9-9.5ml/kg).
- iii. PaO₂/FiO₂<150
1. Invasive mechanical ventilation
 - a. Early appropriate mechanical ventilation
 - b. Lung protective strategy (P plateau <30, Driving Pressure <15 cms H₂O). 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 CO₂ 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/ FiO₂/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, FiO₂ 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



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
SpO₂ 90-94%
PaO₂>55mmHg
PaCO₂<40mmHg
pH>7.3
Pplat<30cmH₂O
DP<15

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

PHENOTYPE H
High elastance (Stiff lung)
High R  L shunt
High PEEP
High Lung weight
High recruitability

*DP=Pplat-PEEP
Avoid BiPAP Machine
@ increase in increments of 2

2. ECMO: Early evaluation & implementation.

i. ECMO Indications: Under optimal conditions

($FiO_2 > 0.8$, 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. $PaO_2/FiO_2 < 50$ for more than 3 hours
- b. $PaO_2/FiO_2 < 80$ for more than 6 hours
- c. $PaO_2/FiO_2 < 100$ with $FiO_2 = 1$
- d. Arterial pH < 7.25 and $PaCO_2 > 60$ mmHg for > 6 hours
- e. Arterial pH < 7.20 and Plateau pressure > 30 cm H₂O 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 ($FiO_2 > 0.9$, Plateau pressure > 30 cm H₂O), 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.

- a. Drainage of airway secretions: Humidification with Heated humidifier /HME. **CLOSED SUCTION** device for Endotracheal suctioning.
- b. Hemodynamic & Volume status: CONSERVATIVE FLUID STATATEGY
 - 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 < 90 mmHg or 40 mmHg less than baseline, MAP < 65 mmHg, 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 PaO₂/FiO₂, Extra vascular lung water if resources permit.
- c. 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.
- d. STEROIDS: As mentioned in medical management of COVID patient.
- e. 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, SpO₂ >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. 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 FiO₂ 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 EtCO₂)
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 H₂O 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 H₂O 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. 40cmH₂O for 40-60 seconds
2. 3 consecutive sighs/min with a plateau pressure of 45cmH₂O
3. 2 minutes of peak pressure of 50cmH₂O and PEEP above upper inflection point (obese/trauma patients may require >60-70cmH₂O)
4. long slow increase in inspiratory pressure up to 40 cmH₂O (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

Recognise 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, eyeshield 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
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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. Romitti 1 , L. Brazzi 4 , L. Camporota
7. Gattinoni et al, 2020 – Covid-19 Does Not Lead to a “Typical” ARDS -INTENSIVE Review Aidan Burrell

FiO₂-PEEP TABLE

Lower PEEP/higher FiO ₂								
FiO ₂	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO ₂	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

10. 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 lower susceptibility or higher incidence of asymptomatic disease in children. 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.

COVID suspect

All symptomatic children (cough / sorethroat / URI / Diarrhea / shortness of breath with or without fever) who have

- 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.
- history of contact with suspected or confirmed case of Covid 19 in last 14 days prior to symptom onset.
- severe acute respiratory illness in the absence of an alternative diagnosis that fully explains the clinical presentation.

Testing

Indications for sending Nasopharyngeal swab for confirmation of Covid 19 Infection include

- Children suspected of having Covid infection, fulfilling the above criteria.
- Patients admitted with severe acute respiratory infection (SARI) irrespective of travel or contact history.
- Asymptomatic direct and high risk contacts of a confirmed case should be tested once between day 5 and 14 of coming in contact with the case (pooled RT – PCR).
- Children from containment zone with ILI.
- Children admitted in hospital with any other disease, who develop influenza like illness (ILI) in the hospital.
- Family clusters of ILI (2 or more cases)
- ILI in high risk population (children with comorbidities).
- Patients posted for elective surgeries (pooled RT – PCR) and emergency surgeries .

Covid 19 testing platforms

The preferred sample is nasopharyngeal. Nasal, throat swabs, ET aspirates and bronchoalveolar lavage may also be tested. The various methods of testing for Covid 19 include RT PCR: This is the gold standard for detecting Covid - 19 cases. It takes 4- 5 hours for running the test. Up to 96 samples are tested at time. Nasaopharyngeal swabs need to be transported in viral transport medium maintaining cold chain.

Pooled RT PCR: Pooled samples of 5 patients are tested by RTPCR. If positive then individual testing is done by RT PCR to identify and confirm disease in the affected. For this samples are collected in tubes containing 0.5ml of viral transport medium.

CBNAAT: It has a quick turnaround time of 30 - 60 minutes but only 1- 4 samples can be tested at a time. For CBNAAT, the samples may be sent in the standard viral transport medium. By far it is the costliest of the molecular tests for Covid.

TrueNat: It is an indigenously developed portable version of CB NAAT. It is the cheapest of the molecular based tests for covid - 19. Swab samples are collected in viral lysis buffer, hence biosafety and biosecurity requirements for use of TrueNat machine is minimal. It comprises of two steps (ICMR guidelines may 2020)

Step 1: screens for E gene. If negative it is considered true negative. If positive needs confirmation by step 2 assay.

Step 2: confirmatory assay for RdRp gene . All positives are taken as true positive and further confirmation by RT PCR not required.

Rapid antigen test: It is a point of care test which yields result in 15 - 30 minutes. Its sensitivity ranges from 50- 84% and specificity 99-100%. So those positive do not need a retesting, but those negative may not be real true negatives. Hence if suspicion is high, needs retesting with RT PCR.

IgG antibody test: It is only for surveillance and not for diagnosis. It helps to detect seroprevalance to plan public health interventions. May be done in high risk or vulnerable population to know who has been infected in the past.

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. There is limited timeline data for infections in children. Adult literature suggests admission to hospital occurs approximately 7 days following symptom onset with onset of severe respiratory distress symptoms approximately 9 to 12 days after symptom onset. 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 rhinorrhoea 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. In study from china of > 44000 persons with Covid, 81% of infections were mild (mild symptoms upto mild pneumonia), while 14% had severe symptoms like hypoxia, dyspnea or > 50% lung involvement in chest xray, while 5% had critical illness (respiratory failure, shock or multiorgan failure). Studies in children have reported fewer severe (5%) and critical illness (0.6%) (3)

Multisystem inflammatory syndrome in children (MIS-C) may occur weeks after a patient is infected with Covid-19(4). MIS – C should be considered in any individual less than 21 years of age 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.

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 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

There is no conclusive data on possibility of reinfection with SARS COV- 2. Viral RNA shedding decreases with resolution of symptoms but may continue for days to weeks. Median range of viral shedding in hospitalised 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.

Triage

Hospitals should preferably establish a 3 tier triage system. At the point of first contact which is often the out-patient counter or hospital entry in case of non emergency patients, history of international travel or travel to hotspot areas with community trans- mission in the last 14 days or contact with suspected or confirmed cases should be elicited and all those with positive history should be directed to the Covid isolation area. Patients with positive history and their care takers should be offered a triple layer surgical mask and directed to the designated Covid isolation areas. In the Covid isolation areas the patients should be triaged for severity of infection.

Patient placement :

- Patients may be admitted in single rooms or in designated Isolation wards.
- There should be a double door entry with changing room and nursing station.
- All healthcare workers should use PPE (N95 mask, eye protection, gloves and gown) when entering a patient room and remove PPE when leaving.
- If possible, use either disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs and thermometers). Equipment which is reused should be disinfected appropriately. Place an appropriate container with a lid outside the door for equipment that requires disinfection or sterilization.
- Avoid patient movement and transport unless absolutely necessary.
- Aerosol-generating procedures (i.e. open suctioning of respiratory tract, intubation, bronchoscopy, cardiopulmonary resuscitation) whenever possible, should be done in adequately ventilated single rooms, preferably negative pressure rooms with minimum of 12 air changes per hour or at least 160 litres/second/patient in facilities with natural ventilation. These rooms may have standalone air-conditioning. These areas should not be a part of the central air-conditioning. If air-conditioning is not available negative pressure could also be created through putting up 3-4 exhaust fans driving air out of the room. These procedures should be done after donning complete PPE, including gloves, long-sleeved gowns, eye protection, and fit tested particulate N 95 masks.
- Used PPEs should be disposed off as per the BMWM guidelines. Ensure these bins (dirty) are inside the isolation areas.

Clinical Management

All children with suspected COVID infection should be categorised into 3.

Category	Clinical features	Clinical severity	Treatment
Category A	Mild sore throat, cough, rhinorrhea, diarrhoea, vomiting	Mild	Symptomatic treatment. Avoid NSAIDS other than paracetamol. Use oral bronchodilators or MDI for those with wheeze. Maintain adequate hydration. ORS and zinc for those with diarrhoea and vomiting

Category B	Fever, severe sore throat, increasing cough Category A symptoms in children with chronic heart, kidney, lung, neurological or liver disease and children on long term steroids, congenital or acquired immunosuppression.	Mild	Oseltamivir 3mg/kg/dose BD till nasopharyngeal swab results are available if criteria for treatment of ILI fulfilled.
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Categorisation based on disease severity

Patients may be further categorised also based on disease severity according to the national guideline June 2020.

Mild: uncomplicated upper respiratory infection with fever, sore throat, rhinorrhea etc without breathlessness or hypoxia.

Moderate: Children with features of pneumonia without danger signs (Respiratory rate : < 2 months: ≥ 60 /mt ; 2–11 months: ≥ 50 /mt ; 1–5 years: ≥ 40 /mt), spo2 90- 94%

Severe: spo2 < 90%, presence of danger signs like inability to feed, grunting, lower chest in drawings, altered sensorium, seizures etc.

Mildly symptomatic patients (Category A):

Patient placement: These patients can be sent home or to CFLTC with supportive treatment. They can also be treated at community health centres, district and sub district hospitals. They should stay away from elderly people, pregnant ladies, other children and patients with comorbidities (5). Clean frequently touched surfaces with 1% Sodium hypochlorite solution and toilet seats with household bleach or phenolic disinfectants. Wash linen separately with detergent and dry. Patient should follow strict personal hygiene including frequent hand washing and use of masks..

Testing

All category A patients with history of contact with a confirmed case of COVID 19 or coming from areas with community transmission should be tested for COVID 19 with nasopharyngeal swab RT PCR.

Treatment

- Symptomatic treatment: Avoid giving NSAIDS other than paracetamol for fever.

- Provide oral bronchodilators or MDI with spacer and mask for children with wheeze. Use of nebulisers should be avoided due to the risk of aerosolisation. Even though it is unclear if visible aerosols come from patients airway during nebulisation.
- Ensure euvolemia. Advise adequate fluid and feed intake. Provide advice regarding use of ORS and other home available fluids in case of diarrhoea and vomiting
- Categorisation should be reassessed every 24 -48 hours.

Category B patients

(patients with fever/increasing cough/ category A symptoms in patients with comorbidities)

Patient placement

These patients need admission. All category B patients should be admitted in single rooms or designated Covid isolation areas.

Monitoring

Daily monitor vitals including spo2, work of breathing and temperature.

Testing

Nasopharyngeal swabs must be sent for confirmation of disease by RT PCR in viral transport medium maintaining cold chain.

Chemotherapeutics

Children with ILI who fulfill the criteria for treatment can be started on Oseltamivir 3mg/kg/dose BD till nasopharyngeal swab results are available.. Antibiotics may be started as per treating physicians discretion if deemed necessary to cover community acquired pneumonia including atypical pneumonia according to local antibiogram. Once swab report is available and diagnosis confirmed Oseltamivir may be stopped. Ivermectin and favipiravir should not be used in children for COVID 19 treatment. In children with moderate/severe disease intravenous remdesivir may be considered on compassionate ground.

Moderate symptoms (Category C)

Admit these patients preferably in dedicated Covid care hospitals, District hospitals, Medical colleges or other tertiary care hospitals catering to Covid patients.

Send nasopharyngeal swab for confirmation of Covid 19 infection.

Respiratory support

Give supplemental oxygen therapy immediately to patients with SARI and respiratory distress or hypoxaemia (Spo2<94%) .

Target Spo2 92- 96% for patients on oxygen therapy (6)

Nasal prongs or cannula are preferred in children as it may be better tolerated.

Offer surgical mask or hood covered by surgical mask to decrease risk of aerosolization and droplet spread.

If on prongs and SpO₂ less than 92% with minimal respiratory distress, options include

- a. Face mask at flow > 5LPM (Fio₂ 40 - 60%)
 - b. Oxygen hood at flow > 5LPM (Fio₂ 30-90%)
 - c. Venturi mask (28 -60% Fio₂)
 - d. Non rebreathing mask at flow 10 - 15LPM (Fio₂ 80 - 90%)
- Awake proning has been advised as a rescue therapy in adults. Typical protocols include 30–120 minutes in prone position, followed by 30–120 minutes in left lateral decubitus, right lateral decubitus, and upright sitting position. Doing proning in children may be more difficult and needs close supervision

Investigations

For patients with respiratory signs and symptoms especially those on oxygen therapy, take chest xray. HRCT may pick up lesions before X ray but may not be feasible to take in all settings.

Daily: 12 lead ECG, CBC with absolute lymphocyte count (Lymphopenia is rare in children), RFT, LFT (SGOT, SGPT, PT INR, S Bilirubin).

Once in 48 to 72 hours: ferritin, D Dimer, CRP.

Monitoring

Monitor for worsening of symptoms like increased work of breathing, increasing oxygen demand or shock.

Drug treatment

If patient is on oxygen support -

- Remdesivir 5mg/kg IV (max. 200mg) loading dose over 30 - 120 minutes on day 1 followed by 2.5mg/kg (max.100mg) IV OD on days 2- 4.
- Start methyl prednisolone IV 1mg - 2 per kg per day.
- Prophylactic low molecular weight heparin may be started if no contraindication at a dose of 1mg/kg s/c OD.

Favipiravir used in adults, is not yet licensed by DGCI for use in children. It is a teratogenic drug hence contraindicated in pregnancy. Favipiravir may be given in a case to case basis if deemed necessary after state medical board concurrence .

Category C patients (severe and critical disease)

Patient Placement

According to the severity of disease these children may require either HDU or ICU care. Depending on the infrastructure, patient load and staff competence in managing sick children patient placement may vary from institution to institution. All children with moderate to severe

ARDS (P/F ratio less than 200 / OI >8 / OSI > 7.5 while on CPAP of minimum 5 cm), shock, multi organ involvement and those with Spo2 < 94% with increased work of breathing (> 2site retraction/ paradoxical breathing / see saw breathing / head bobbing etc.) should be preferably admitted in PICU

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 which may later progress to involve the whole lung fields.

Risk markers : CRP, D Dimer, Ferritin, Troponin I. Send these in all patients with severe or critical disease admitted in HDU or PICU every 48 hrs and in those with worsening respiratory status. D Dimer may be sent in in all those with hypoxia to look for evidence of microthrombi formation especially in pulmonary vasculature con- tributing to hypoxia. 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 - 10,000mcg/L), falling counts, rising or falling ESR, increasing CPK, LDH and new onset shock especially with elevated Top i/ TropT.

Tocilizumab:

Cytokine storm is an important cause of worsening of respiratory status with multi organ failure. Criteria for patients at high-risk for developing cytokine storm include Ferritin >300 ug/L with

doubling within 24 hours , Ferritin >600 ug/L at presentation, CRP > 100 mg/L, LDH >250 and Elevated D-dimer (>1 mg/L) . Consider cytokine storm in patients with rapidly worsening respiratory gas exchange, radiographic infiltrates by imaging (chest x-ray, CT scan, etc.) and SpO₂ ≤93% on room air or on greater than 6 L/min O₂.

Tocilizumab in combination with steroids is now recommended in patients with

1. Recently hospitalized patients who have been admitted to ICU within the prior 24 hours and who require invasive mechanical ventilation, NIV or HFNC [>0.4 FiO₂/30L/min of oxygen flow]

OR

2. Recently hospitalized patients with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation [CRP >75 mg/L]

Pediatric Dosing (<18yrs): < 30kg – 12mg/kg IV in 50 -100ml normal saline over 60 minutes
> 30kg - 8mg/kg IV over 60minutes (max. 800mg per infusion).
Adult dose : 400mg IV over 60 minutes

Consider giving additional 2 dose 8-12 hours later if continued clinical decompensation
Contraindications: Avoid in pregnancy and newborns. Mothers should stop breast feeding, if receiving tocilizumab Monitor liver enzymes in patients receiving tocilizumab. Serious adverse events: Gastrointestinal perforation, Anemia, Hepatitis, Infusion reaction

Steroids

Steroids may be considered in patients requiring oxygen support Dose: Methyl Prednisolone 1-2mg/kg/day for 5- 7 days. It may also be given to patients with grade 3 or 4 CRS with worsening respiratory status who cannot afford Tocilizumab. It may also be considered in patients with catecholamine refractory shock

Respiratory support in severe cases

If a saturation of > 95% is achieved by flow of 15LPM oxygen, it indicates the shunt fraction is mild. Failure to achieve this indicates a moderate-severe shunt fraction. These children should be closely monitored for deterioration and respiratory support to be escalated as per need.

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.

- Switch on the machine only after fixing the nasal cannula.
- Start at 0.5 - 1litre per kg per minute and increase upto 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.

Jackson Rees with cushioned mask: It can provide oxygen at high fio₂ and requires lesser oxygen flow than Baines circuit as dead space less. It also provides peep with minimal aerosolisation. It can be fixed using harness.

NIV CPAP: 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 pa-ent 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 / pa-ent in areas with natural ventilation and then shift to main ICU preferably with the same facility to minimise aerosol genera-on and expo- sure 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 antisialagogue 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

SpO₂ 90 – 94%, pH > 7.3 , P plateau < 28 (<31 if chest wall oedema plus) and driving pressure less than 15 cm H₂O. 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 H₂O. 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 H₂O 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 FiO₂ >0.6 and PEEP >5 cm H₂O. Keep prone for 16 -18 hours if possible.

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 30 Mts 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 adults Norepinephrine preferred while in children adrenaline is the initial inotrope of choice) in fluid refractory shock. Further titration depends on hemodynamic parameters.
- Noradrenaline may be added to adrenaline if hypotension persists inspite of fluid and adrenaline.
- In patients with evidence of cardiac dysfunction and persistent hypoperfusion in spite of fluids and norepinephrine add dobutamine over increasing dose of nor- epinephrine.
- In case of catecholamine refractory shock low dose hydrocortisone 2- 4mg/kg/ day may be used as continuous infusion or intermittent dose.
- Specific therapy: No specific antiviral therapy is definitely proven to be effective as per current available literature. Drugs being used in clinical trial settings include
 - ▶ Remdesivir

- ▶ Nitazoxanide
- ▶ Ivermectin
- ▶ Favipiravir

Remdesivir

EUA (emergency use authorisation) has been granted by FDA for use in children and adults with severe disease. It is yet to be approved by DGCI for use in children, hence should be administered only after written consent and medical board concurrence. Indicated in category C patients with moderate and severe illness on respiratory support.

Dose : 5mg/kg IV (max. 200mg) loading dose over 30 - 120 minutes on day 1 followed by 2.5mg/kg (max.100mg) IV OD on days 2- 4.

Duration of treatment: Usual duration 5 days. If no clinical improvement, duration may be extended to total 10 days.

Contraindications: AST/ALT > 5 times above upper limit of normal. Severe renal impairment, pregnancy and lactation.

Convalescent plasma

It may be considered as per state protocol for patients with moderate and severe disease. It is an off label use. It should be avoided in patients with IgA deficiency or immunoglobulin allergy. According to ICMR guidelines ABO compatible cross matched plasma with neutralising titre above the threshold level or plasma IgG titre against S - protein RBD above 1: 640 should be used.

Dose 10ml/kg.

Follow up sample and discharge

1st follow up sample is to be taken on the 10th day from the 1st day of positivity for asymptomatic and category A and B patients. For category C patients 1st follow up sample to be taken on the 14th day from the 1st day of positivity.

If test remains positive on day 14 repeat testing every alternate days till negative. The patient may be discharged if he/she has completed 14 days since onset of symptoms and no symptoms since last 3 days and test is negative.

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11. Multisystem inflammatory syndrome in children (MIS-C)

Multisystem inflammatory syndrome is one of the common Covid presentations in children usually presenting weeks after acute infection. MIS-C may have three presentations: MIS-C without overlap with acute COVID-19 or Kawasaki Disease, MIS-C overlapping with severe acute COVID-19 and MIS-C overlapping with KD

The case definition for MIS-C is:

- Fever with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) and
- laboratory evidence of inflammation and
- no alternative plausible diagnoses and
- positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

Common symptoms at presentation include fever, abdominal pain, vomiting, diarrhea, polymorphous rash, non purulent conjunctivitis, cardiogenic shock, cervical lymphadenopathy, neurocognitive symptoms, swollen hands and feet etc.

Many children with MIS-C meet the criteria for complete or incomplete Kawasaki Disease. MIS-C commonly affects older children and adolescents whereas classic KD typically affects infants and young children.

Positive inflammatory markers include one or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, ferritin, D Dimer, LDH, interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin. Most children also have elevated Troponin T and NT pro BNP.

Children may be positive for SARS COV2 infection by RT PCR, antigen test, antibody test or may have history of exposure to suspected or confirmed case of Covid 19 case within 4 weeks prior to onset of symptoms.

Investigations

- In Patients with mild symptoms send Complete blood count including ESR, CRP, Electrolytes, S Albumin
- ESR > 40mm in 1st hour or CRP > 60mg/L and any one of the following
 - ALC < 1000/mm³,
 - Platelet < 1.5laks/mm³
 - Na < 135meq /L
 - Neutrophilia
 - Hypoalbuminemia

send second line investigations

- Second line Investigations: Ferritin, D Dimer, Troponin T/i , NT pro BNP, LDH, IL- 6 (if available), and organ functions RFT, LFT, PT INR, Echocardiography
- Echo to look for coronary artery aneurysm, systolic and diastolic dysfunction.
- RT PCR and serology for evidence of SARS COV2 infection.
- Send for blood and urine culture. Investigations for Dengue, leptospirosis, Scrub typhus may be sent where indicated to look for alternate causes of fever.

MANAGEMENT

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.

Empiric antibiotic for patients presenting with fever and critical illness(ceftriaxone + clindamycin).

Immunomodulation

IVIg (2g/kg) administered in a single dose infusion over 8-12 hours for patients presenting with features of KD or coronary dilatation especially younger age group. For patients with severe LV dysfunction it can be given over 2 - 3 days if single day administration not feasible due to fluid overload and cardiac dysfunction.

MIS-C patients presenting with shock especially in higher age group who are antibody positive may be treated with methyl prednisolone 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. IVIG may be given in non responding cases.

Refractory disease (persistent fever for > 36 hrs after 1st dose of IVIG) 2nd dose IVIG at 2gm/kg may be given with steroids (30mg/kg/day for 3 days).

Anakinra (>4mg/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

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 patients with MIS-C and continued for 4-6 weeks until normalization of platelet count and confirmed normal coronaries at ≥ 4 weeks

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.

Patients with MIS-C and documented thrombosis or an ejection fraction (EF) <35% should receive therapeutic anticoagulation with enoxaparin 1mg per kg BD SC, followed by warfarin until at least 2 weeks after discharge from the hospital.

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

MIS-C patients with a coronary artery z-score ≥ 10.0 should be treated with low dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xa level 0.5-1.0) or warfarin

Mild MIS-C

Patients with high inflammatory markers (including D Dimer more than twice upper limit of normal) with fever without evidence of organ failure should be closely monitored for new onset symptoms and signs of organ involvement and inflammatory markers repeated after 48 hours . If markers persistently high with no fever aspirin at anti platelet dose (3-5mg/kg/day) may be started with reassessment with echo at 4-6 weeks.

In patients with fever, high inflammatory markers and positive covid antibody test without organ involvement, if fever persists at 48hrs with persistently high inflammatory markers without evidence of organ involvement prednisolone 2 mg/kg/day may be given for 10 days followed by 1mg/kg/day for 5 days along with aspirin at anti platelet dose. These children should be followed up with echo at discharge and at 6 weeks.

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.

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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12. 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 ≥ 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, 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 endocarditis, auto immune conditions like SLE, vasculitis etc

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.

Rule of the thumb

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

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

Treatment

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

1. Inj Methyl prednisolone
2. IVIg
3. Inj Tocilizumab

13. 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 hyperglycemic emergencies like Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic 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
- 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

	A	B	C	E	F
	COVID CAT A	COVID CAT B	COVID CAT C / ON STEROIDS	NASOGASTRIC FEEDS	ON PARENTERAL NUTRITION ONLY
Non-Diabetic	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
Diabetic with reasonable control on admission (FBS<140 mg%, PPBS <180 mg% Hba1c <8 %)	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 th hourly RBS
Uncontrolled diabetes (FBS > 140, PPBS> 180, HbA1c >8)	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

Dangerously uncontrolled Diabetes (Any RBS value > 400 mg/dl)	<ul style="list-style-type: none"> - Check urine ketones and VBG - Insulin infusion for RBS control - If acidosis / ketosis +, manage DKA as per standard protocol - Refer the 'section on Insulin infusion' for detailed description
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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 / Teneeligliptin / 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 regimen

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
-

Patients and glycemic profile	Initial total Daily Dose (units/kg body weight)
<u>Known Diabetes mellitus on Insulin + OHAs</u> Diabetes on treatment with reasonable control (FBS <140, PPBS < 180 on admission)	- 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
Diabetes on treatment which is uncontrolled(FBS > 140,PPBS > 180, HbA1c > 8)	- Dosage increased by 25% from the estimated TDD
On oral agents / life style therapy with HBA1C < 7 %	✓ Needs corrective insulin dose only ✓ If blood glucose consistently > 140 mg/dl, add basal insulin at 0.1 U/kg
Use of steroids	
Diabetes with reasonable control (FBS <140, PPBS < 180 on admission)	Dosage increased by 25% from the estimated TDD
Uncontrolled diabetes on admission(FBS > 140,PPBS > 180)	Dosage increased by 50% from the estimated TDD (to be tapered as steroid doses are weaned)
Newly diagnosed Diabetes mellitus	
Age ≥ 70 / eGFR < 60 ml/min/1.73m²	0.2 – 0.3 U/kg
DM with glucose 140-200 mg/dl or HBA1C 8-9.9%	0.4 U / kg
DM with glucose 200 – 400 mg/dl or A1C ≥ 10%	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 1.3rd 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 nasogastric feeding
- Total parenteral nutrition
- DKA / HHS
- Peri-operative period
- Labor and delivery

Infusion protocol

- Strength 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 **7** divide by 100 and round off to nearest 0.5 for initial infusion rate (without bolus)
- If initial blood glucose \geq 300 **7** divide by 100 and round off to nearest 0.5 for initial 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

	COVID CAT A/B/C taking food by mouth (with or without steroids)	COVID CAT B/C on nasogastric feeds (with or without steroids)
Underweight (BMI < 18.5 kg/m²)	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
Normal weight (BMI 18.5- 23 kg/m²)	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
Overweight (23-27 kg/m²)	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
Obese (> 27 kg/m²)	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

			Treatment
Conscious; on oral feeds		BG: 50-69 mg/dl	15-20 gm simple CHO
		BG: < 50 mg/dl	20-30 gm simple CHO
Conscious; but NPO		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
Unconscious		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 patients had received corrective insulin before the event, consider increasing sensitivity factor of corrective insulin