



STNM HOSPITAL

COVID-19

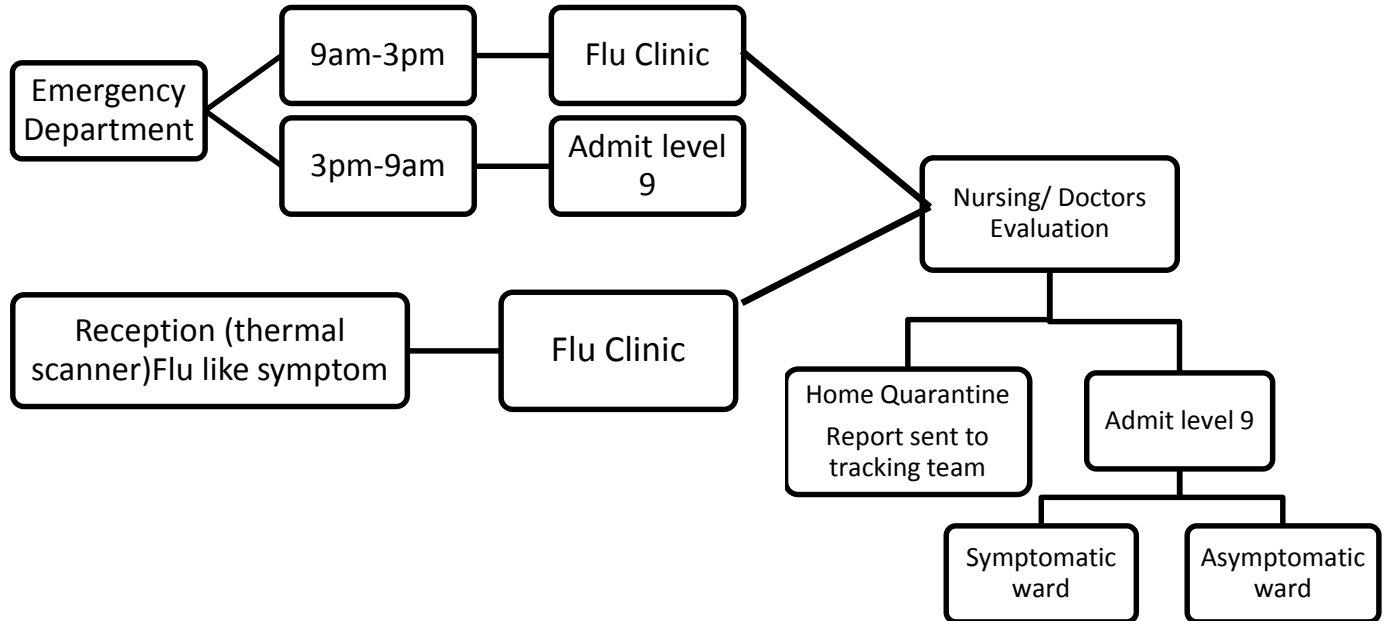
**STANDARD OPERATING
PROCEDURE**

AND

TREATMENT PROTOCOL

Passed by the Technical Committee
for COVID-19 control

PATIENT FLOW PROTOCOL

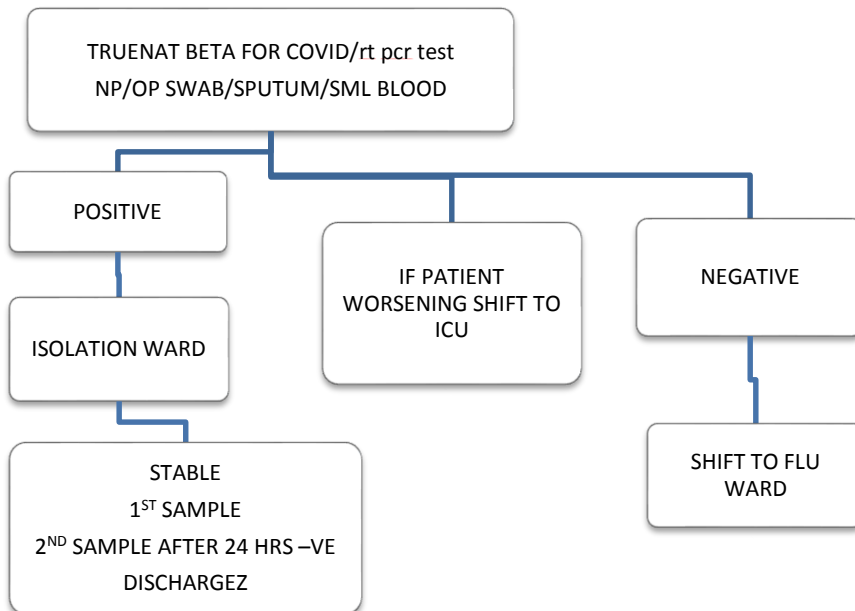
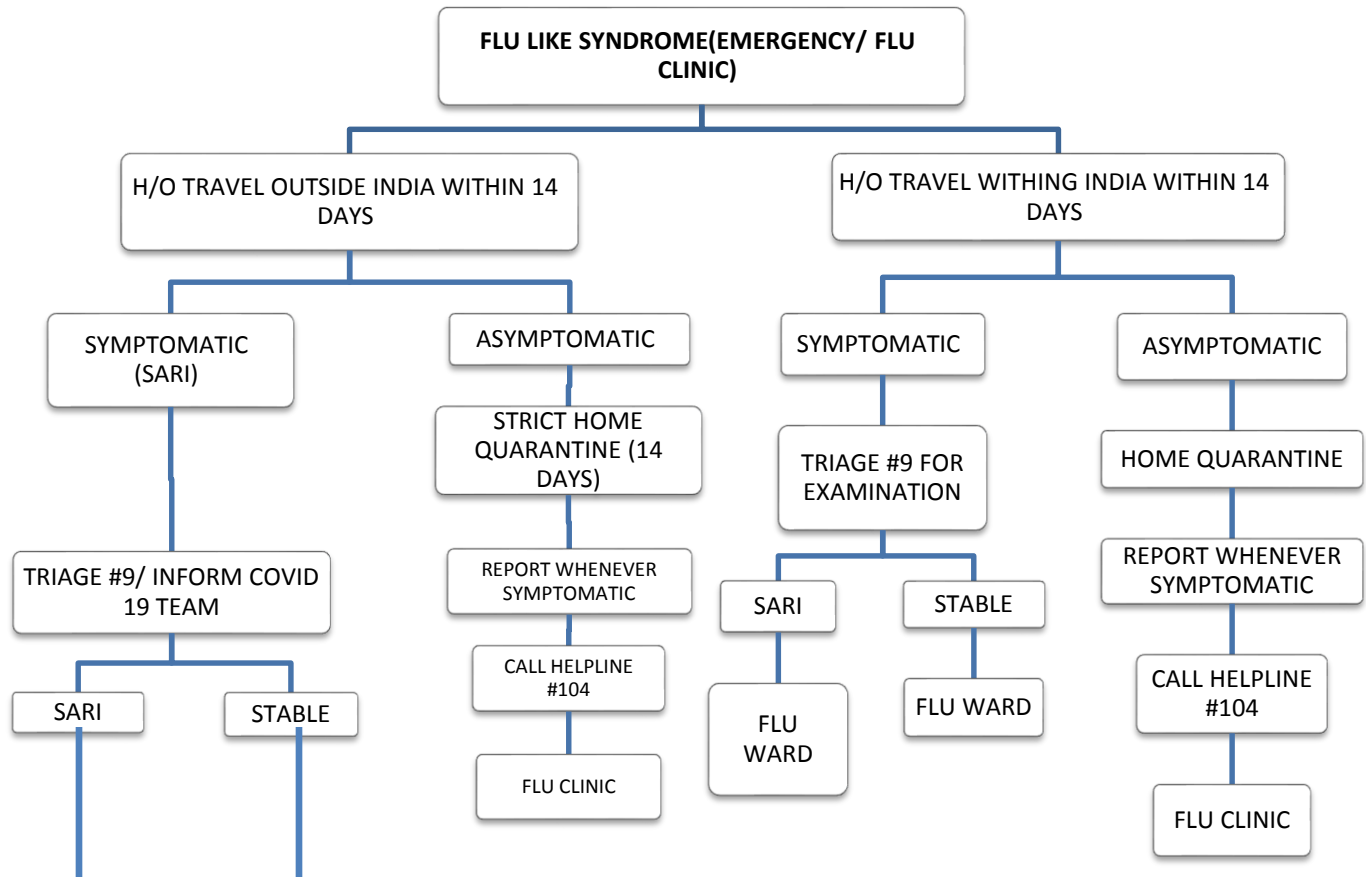


Significant History

- h/o Travel abroad or within India
- h/o contact Covid-19 positive
- h/o flu like symptoms with or without co- morbidities
- SARI/ILI
- Health workers exposed to ILI &SARI symptomatic

SANITARY ATTENDANT: A MUST TO SANITIZE AT ALL LEVELS, 2HRLY

PROTOCOL FOR SUSPECTED PATIENT MOVEMENT



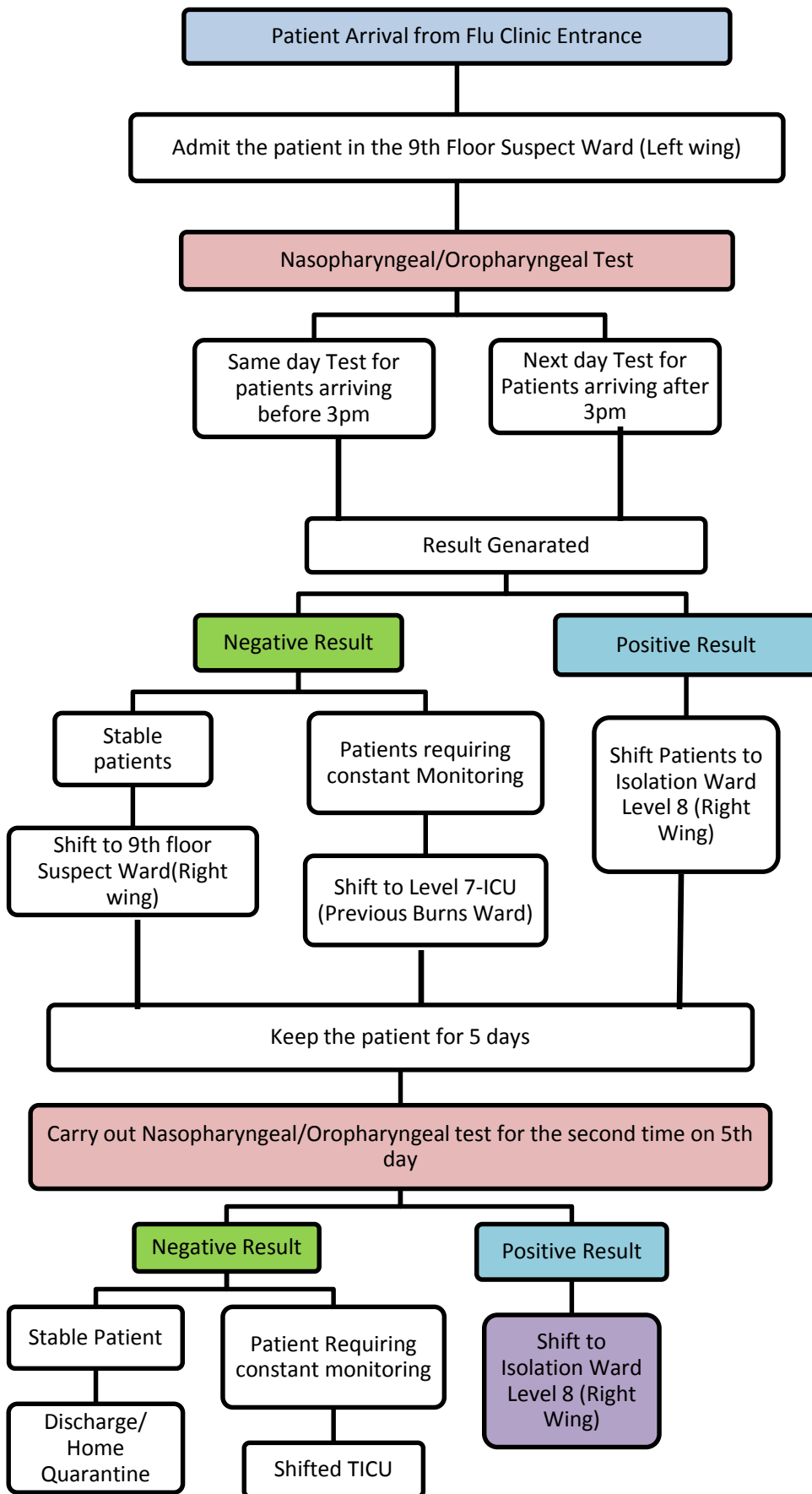
- ICU CRITERIA**
- RESPIRATORY FAILURE
 - HYPOTENSION
 - WORSENING MENTAL STATUS
 - MODS

- COVID-19 (ISOLATION TEAM FIRST LINE)**
- NODAL ODDICER
 - MEDICAL SPECIALIST ON CALL
 - ENT SPECIALIST ON CALL
 - MICROBIOLOGIST ON CALL

COVID-19

Management of sick patients coming from out of State

Process Flow:



FLU CLINIC ADVISORY

STANDARD OPERATING PROCEDURE IN EMERGENCY

PATIENT IN ER/FLU CLINIC



PROVIDE A SURGICAL MASK TO EVERY PATIENT

AND

MAINTAIN 1 METER DISTANCE FROM EACH OTHER



SCREENING BY DOCTOR WEARING PROTECTIVE GEAR



SL NO.	HISTORY	SCORE
1.	TRAVEL HISTORY	3
2.	CONTACT WITH COVID-19	3
3.	FEVER &/OR MYALGIA	1
4.	DRY COUGH	1
5.	SHORTNESS OF BREATH	1
6.	HISTORY OF SIMILAR SYMPTOMS IN FAMILY/FRIENDS	1
7.	HEALTH CARE WORKER	1
8.	SORE THROAT	1
9.	ANOSMIA (LOSS OF SMELL)	1
10.	DIARRHOEA	1
11.	CONJUNCTIVITIS	1
12.	HEADACHE	1
13.	AGEUSIA (LOSS OF TASTE)	1
14.	SKIN RASH	1
15.	INFLAMMATION OF TESTIS	1
16.	MYALGIA	1
17.	CHILLS	1
18.	SUDDEN ONSET CONVULSIONS	1

SCORE

≤ 3.....HOME QUARANTINE FOR 14 DAYS.

4-8.....HOSPITAL QUARANTINE FOR 14 DAYS

≥ 9.....SHIFT TO CORONA SUSPECT WARD LEVEL 8

CATEGORIES OF COVID-19 PRESENTATION

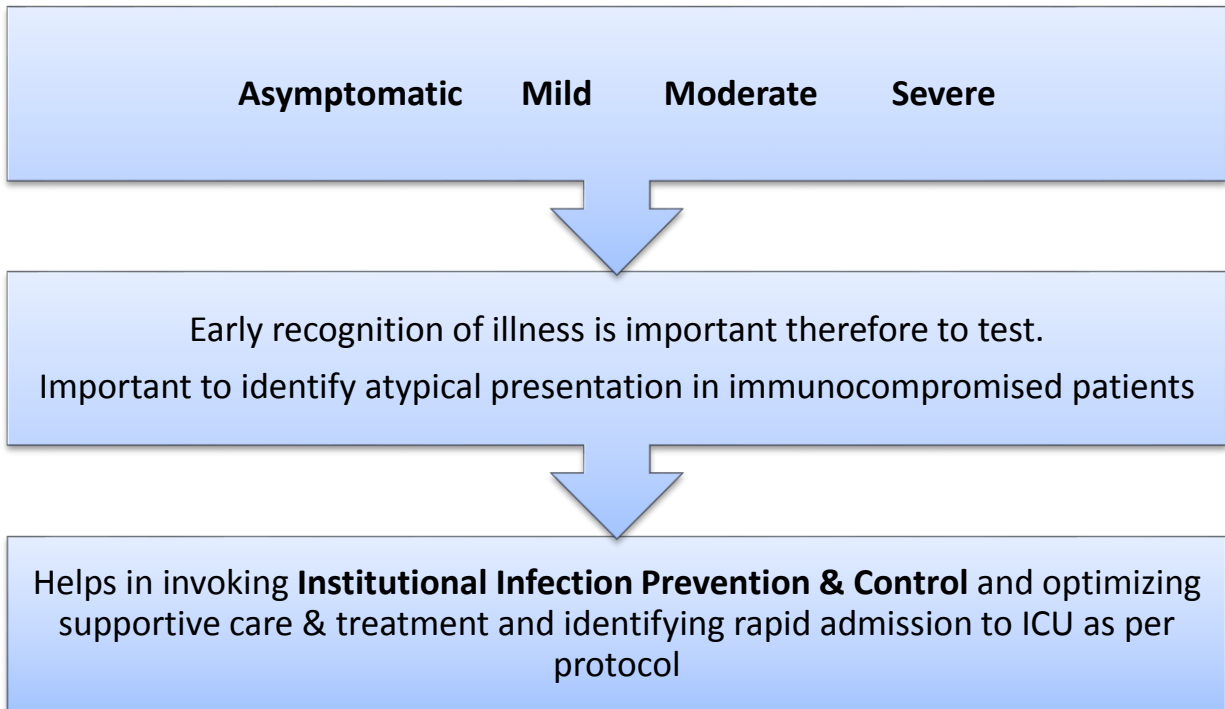
A	Mild sore throat/cough/rhinitis/diarrhea
B	<p>Fever and/or severe sore throat/ cough/ diarrhea OR Category A....plus 2 or more of the following</p> <ul style="list-style-type: none"> • Lung/heart/liver/kidney/ neurological disease/ hypertension/ hematological disorder/ uncontrolled diabetes/ Cancer/ HIV AIDS • Patient on long term steroid/ immunosuppressive drugs. • Pregnant lady • Age>60 years <p>OR Category A....plus CVS disease</p>
C	<ul style="list-style-type: none"> • SOB, Chest pain, Drowsiness, Fall in BP Hemoptysis, Cyanosis • Children with ILI with red flag signs i.e. (Somnolence, high persistent fever, inability to feed well, convulsions, dyspnoea/ respiratory distress) • Worsening of underlying chronic conditions

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

IDENTIFICATION OF HIGH RISK PATIENT

CO-MORBIDITIES	CLINICAL ASSESSMENT	LABORATORY VALUES
Uncontrolled Diabetes	Hypoxia – SpO2 ≤ 93% on room air	CRP>100mg/L
Hypertension	Tachycardia PR > 125/min	CPK> twice upper limit of normal
Cardiovascular Disease	Respiratory distress RR> 30/min	
Lung Disease	Hypotension BP< 90/60	Ferritin > 300mcg/L
CKD	Altered Sensorium	Troponin T elevation
CLD		LDH > 245 U/L
On Immunosuppressives		D Dimer > 1000ng/ml
HIV / Congenital Immunodeficiency Disorder		Multi organ dysfunction
Age > 60 years		Absolute Lymphocyte Count < 0.8

PRESENTATIONS OF COVID - 19



- Mild illness hospitalization not required unless rapid deterioration
- All patients discharged for home quarantine should be advised to report to hospital in case of worsening illness or call 104.
- Severe illness means severe pneumonia, PLEF, ARDS, Sepsis & Septic Shock

INFECTION PREVENTION CONTROL (IPC)

- Critical and Integral part of clinical management.
- Need initiation at point of entry of patient to hospital.
- Standard precaution implementation like hand hygiene, use of PPE
- Avoid contact with blood, body fluid secretion and non-intact skin
- Prevention of needle stick or sharp injury
- Safe waste management
- Cleaning and disinfection of equipments and environment.

IMPLEMENTATION OF IPC IN SUSPECT OR CONFIRMED COVID - 19

<p>At Triage</p>	<ul style="list-style-type: none"> • Triple layer surgical mask and keep patient in separate area • Minimum 1m distance between suspect and other patients • Instruct elbow nose mouth cover during coughing and sneezing • Hand hygiene/wash with soap water
<p>Apply droplet precautions</p>	<ul style="list-style-type: none"> • Triple layer mask. Maintain 1-2m distance or group patients together with same etiological diagnosis • Eye protection (face masks or goggles) • Limit patient movement in hospital • Foot wear sanitation disinfection with 1% hypochlorite solution
<p>Apply contact precautions</p>	<ul style="list-style-type: none"> • Use PPE (donning and doffing) • Dedicated equipment like stethoscope, BP cuff, thermometer • Refrain HCW from touching eyes, nose and mouth with gloved or ungloved hands • Avoid contaminating environmental surfaces (door handles, switches, etc.) • Ensure adequate room ventilation
<p>Apply airborne precautions when performing an aerosol generating procedure</p>	<ul style="list-style-type: none"> • Complete PPE set use with N-95 mask • Sampling in well ventilated rooms • Avoid unnecessary individuals in room

PERSONAL PROTECTIVE EQUIPMENT:

DONNING	DOFFING
1. WASH HAND WITH SOAP & WATER. WEAR GLOVES	1. SANITIZE & REMOVE FIRST GLOVES
2. SURGICAL MASK & HEADGEAR	2. REMOVE PPE & HEAD GEAR INSIDE OUT- SANITIZE
3. WEAR SHOES WITH SHOE COVER	3. REMOVE PPE SHOE COVER- SANITIZE
4. SURGICAL GOWN & PLASTIC APRON	4. REMOVE GOGGLES BENDING FORWARD -SANITIZE
5. GLOVES OVER SURGICAL GOWN (COLOURED)	5. REMOVE MASK (LOWER SIDE FIRST)- SANITIZE
6. FOOTWEAR OF PPE	6. APPROACH DOOR, CLEAN SHOE COVER IN HYPOCHLORITE MAT & REMOVE 1 ST LEG COVER, STEP OUTSIDE
7. PPE	7. REMOVE 2 ND SHOE COVER AND STEP TO CLEAN ZONE
8. SURGICAL GLOVES	8. REMOVE COLOURED GLOVES
9. WEAR N95 & PERFORM MASK FIT-TEST	9. GO TO NEXT ROOM, REMOVE GLOVES & MASK
10. GOGGLES	10. HANDWASH WITH SOAP & WATER
11. PPE HEAD GEAR	11. WEAR FRESH HEAD GEAR, MASK & GLOVES & LEAVE DOFFING AREA
12. WEAR EXTRA HEAD GEAR IF REQUIRED	
13. CHECK FOR LEAKS OR OPEN AREA	

CLINICAL SYNDROMES OF COVID - 19

Uncomplicated Pneumonia	<ul style="list-style-type: none"> • Fever, Cough, Sore Throat, Nasal Congestion, Malaise, Headache • Elderly and immunosuppressed may have atypical symptoms
Mild Pneumonia	<ul style="list-style-type: none"> • Child: Non-severe pneumonia, Cough, Difficulty in breathing, Fast breathing • <2 months, >60/min • 2-11 months, >50/min • 1-5years, >40/min with no signs of severe pneumonia
Severe Pneumonia	<ul style="list-style-type: none"> • Adolescent or adult; Fever or respiratory infection + RR>30/min, SpO2<90% with severe respiratory distress • Child- cough, SOB + Central cyanosis or SpO2<90%, ARDS with pneumonia with inability to eat, drink, lethargy, convulsions, chest imaging required.
Acute Respiratory Distress Syndrome	<ul style="list-style-type: none"> • Onset: New or worsening respiratory symptoms within one week • CXR, CT scan thorax, Lung ultrasound • Identify origin of edema; R/O respiratory failure, cardiac failure, volume overload, need ECHO • Oxygenation: as per protocol
Sepsis	<p>Adults: Organ dysfunction, Signs: altered mental status, SOB, Low oxygen saturation, oliguria, sinus tachycardia, weak pulse, cold extremities, low BP, skin mottling</p> <p style="text-align: center;">OR</p> <p>Laboratory evidence, coagulopathy, thrombocytopenia, lymphopenia, acidosis, high lactate or hyperbilirubinaemia</p> <p>Child: Same as above</p>
Septic Shock	<p>Adult: Persistent low BP requiring vasopressor to maintain MAP>65mmHg. Do not use Dopamine. Only Nor-Adrenaline</p> <p>Child: Hypotension, altered mental state, bradycardia or tachycardia, petechial or purpuric rash, increase lactate, oliguria, hyper/hypothermia</p>

LABORATORY INVESTIGATIONS FOR PROVEN COVID – 19 PATIENTS

On Admission	CBC, KFT, LFT, CRP,RBS, ECG, CXR
If Clinically active and indicated	CXR,HIV, HBsAg, anti HCV, D-Dimer, Ferritin, LDH, CPK, Procalcitonin, Blood Culture
To repeat Every 3 Days if clinically deteriorating	CBC, Creatinine, AST, ALT, CRP, LDH,CPK, Ferritin, CT thorax
Immunocompromised patients eg. HIV, transplant recipients,	Test to rule out opportunistic infections TB, pneumocystis jiroveci, Fungal infections

EARLY SUPPORTIVE THERAPY MONITORING

- a) Supplemental oxygen therapy @5 L/min.

Children SpO₂ >94%

All treatment zones should have O₂ supply, disposable single use O₂ delivering interfaces

- b) Conservative Fluid Management when no evidence of shock

- c) Empiric Antibiotics:

Based on clinical diagnosis, Community acquired pneumonia, health care associated pneumonia, local epidemiology and susceptibility data

Empirical therapy means use of neuraminidase inhibitor for treatment of influenza (only Oseltamivir 75mg available in STNM)

- d) Corticosteroids- not to be used regularly until severe ARDS on/after 5th day of clinical symptoms

- e) Monitor patients with SARI for clinical deterioration. Advocate immediate supportive therapy

- f) Co-morbid conditions to be recorded of patients and treated accordingly

- g) Communicate early with patient and family. Psychiatric intervention.

MANAGEMENT OF HYPOXEMIC RESPIRATORY FAILURE AND ARDS

- ARDS commonly results in Intrapulmonary Ventilation/Perfusion mismatch or shunt requires mechanical ventilation.
- If standard O₂ therapy, high flow nasal cannula O₂ (HFNO) therapy or NIV fails tracheal intubation and mechanical ventilation can be considered in timely manner
- Non Invasive Ventilation (NIV) is contraindicated in patients with hemodynamic instability ,abnormal mental status, Multi Organ Failure (MOF), hypoxemic respiratory failure or pandemic viral illness
- Pre oxygenation with 100% Fio₂ / 5MIN via facemask with reservoir bag
- Mechanical ventilation is implemented using lower tidal volume (4-8 ml/kg predicted body wt) & lower inspiratory pressure (<30cm H₂O).
- Deep sedation may also be considered.
- For patients with severe ARDS ,prone ventilation for >12 hrs /day
- Use conservative fluid management strategy for ARDS pt without tissue hypoperfusion.
- Higher PEEP and recruitment maneuvers [delivering episodic period of high continuous positive airway pressure (30-40 cm of H₂O)] are recommended.
- Consider referral of patient with refractory hypoxemia in expert centre with extracorporeal life support.
- Avoid disconnecting the patient from ventilator. Use in line catheter for airway suction and clamp ET tube when being disconnected.

MANAGEMENT OF SEPTIC SHOCK

- Early Recognition of septic shock in adults and children and following treatment within 1 hr by giving vasopressor to maintain Mean Arterial Pressure ,antimicrobial therapy ,fluid loading.
- Resuscitation:
In adults-30ml /kg of isotonic crystalloid in first 3 hours
In children-20 ml/kg as rapid bolus (40-60 ml/kg in first 1 hr)
- Caution must be taken to avoid volume overload
- Crystalloids include NS and RL.
- Consider dynamic indices such as passive leg elevation, fluid challenges with serial stroke volume measurement or variation in systolic pressure ,pulse pressure during mechanical ventilation
- Administer vasopressors when shock persists during or after fluid resuscitation. Initial MAP \geq 65 mmHg in adults and age appropriate targets in children.
- In absence of central venous catheters use peripheral IV in large vein and closely monitor for extravasation and local tissue necrosis.
- If signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target consider inotrope such as dobutamine

OTHER THERAPEUTIC MEASURES

- Initiate glucocorticoids 3-5 days
Methylprednisolone 1-2 mg/kg/day.
- Severe critical early pregnancy should preferably be terminated in consultation with obstetric, neonatal and ICU specialist
- Anxiety and fear is to be supported by psychological counseling.
- In case of Non availability of hemodialysis, peritoneal dialysis maybe considered.

TREATMENT: Adapted from MOHFW/ AIIMS/ Kerala

Government Protocol

PRECAUTIONS TO BE TAKEN:

1. AVOID using NSAIDs other than paracetamol unless absolutely necessary.
2. AVOID using nebulized drugs to avoid aerosolization of virus, use MDI instead
3. Oseltamivir 75mg 1-0-1 in all symptomatic patients with influenza like illness until PCR report with dose adjustment for pediatric and renal insufficiency
4. Antibiotic selection in case of secondary bacterial pneumonia should be as per institutional antibiogram.
5. AVOID using systemic steroids. Steroids may be considered only in case of refractory shock, macrophage activation syndrome or in Cytokine release syndrome (CRS) Grade 3 or 4 with no response to Tocilizumab.
6. Non- invasive ventilation [NIV] is to be avoided in patients with COVID-19, as there is high risk of aerosol generation as the seal they generate is inferior to that achieved with a correctly placed and inflated cuffed tracheal tube
7. Consider discontinuation of inhaled steroids as they may reduce local immunity and promote viral replication. But if discontinuation of inhaled steroids is likely to worsen the preexisting lung disease, decision on the same has to be taken by the treating doctor.

TREATMENT STRATEGIES ACCORDING TO CLINICAL SITUATION

CATEGORY	TREATMENT	PRECAUTIONS
A	Symptomatic treatment	Categorization should be reassessed every 28-48 hours for Category A.
B	<p>1. Tab HCQs 400mg 1-0-1 x 1 day, then 200 1-0-1 x 4 days (Children : 6.5mg/kg/dose PO BD day 1 followed by 3.25mg/kg/dose PO BD X 4 days) OR Tab Chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5mg/kg) 12h later, followed by 300mg(5mg/kg) BD up to Day 5 Plus</p> <p>2. Tab Azithromycin 500mg 1-0-0 x 1 day and 250mg 1-0-0 x 4 days Children: 10 mg/kg (max 500mg) day 1, Followed by 5mg/kg/day on days 2 to 5.</p> <p>3. Tab Oseltamivir 75mg1-0-1 in all symptomatic patients with influenza like illness until PCR report. Children: 3mg/kg/dose BD dose adjustment for those with renal insufficiency</p>	<p>Contraindications to chloroquine/ HCQS</p> <ul style="list-style-type: none"> • QTc > 500msec • Porphyria • Myasthenia gravis • Retinal pathology • Epilepsy <p>Pregnancy is NOT a contraindication If Baseline QT is prolonged - Frequent ECG monitoring is required</p>
C	<p>1. b HCQs 400mg 1-0-1 x 1 day, then 200mg 1-0-1 x 4 days Children: 6.5mg/kg/dose PO BD day 1 followed by 3.25mg/kg/dose PO BD x 4 days OR Tab Chloroquine base 600mg (10mg/kg) at diagnosis and 300mg (5mg/kg) 12h later , followed by 300mg (5mg/kg) BID up to Day 5. [Usually 1 tablet of chloroquine has 150mg base] PLUS Inj Azithromycin 500mg IV stat and 250mg IV OD for 5 days Children: 10mg/kg (max 500mg) day 1, followed by 5mg/kg/day on days 2-5.</p> <p>2. Tab Lopinavir/ Ritonavir (400/100) 1-</p>	<p>For chloroquine and derivatives as discussed above</p> <p>For Protease inhibitors Assess for drug – drug interactions (including with calcineurin inhibitors) before starting.</p> <p>Gastrointestinal intolerance may be seen</p> <p>Monitor liver function tests while on therapy.</p> <p>Discontinue these agents upon discharge regardless of duration, unless previously</p>

	<p>0-1 for 14 days or for 7 days after becoming asymptomatic.</p> <p>Children:</p> <ul style="list-style-type: none"> • 14 days – 6 months: 16mg/kg (based on lopinavir component) PO BD • <15kg: 12mg/kg PO (based on lopinavir component BD) • 15-25 kg: 200mg-50mg PO BD • 26-35 kg: 300mg-75mg PO BD • >35 kg: 400mg-100mg PO BD <p>Lopinavir / Ritonavir is to be used only if HCQS/ Chloroquine is contraindicated. Lopinavir/Ritonavir should be used only on a compassionate ground after informed consent. It has to be started within 10 days of symptom onset.</p> <p>3. Tab Oseltamivir 75mg 1-0-1 in all symptomatic patients with influenza like illness until PCR report with dose adjustment for children and those with renal insufficiency</p>	<p>used as maintenance medications for another indication.</p>
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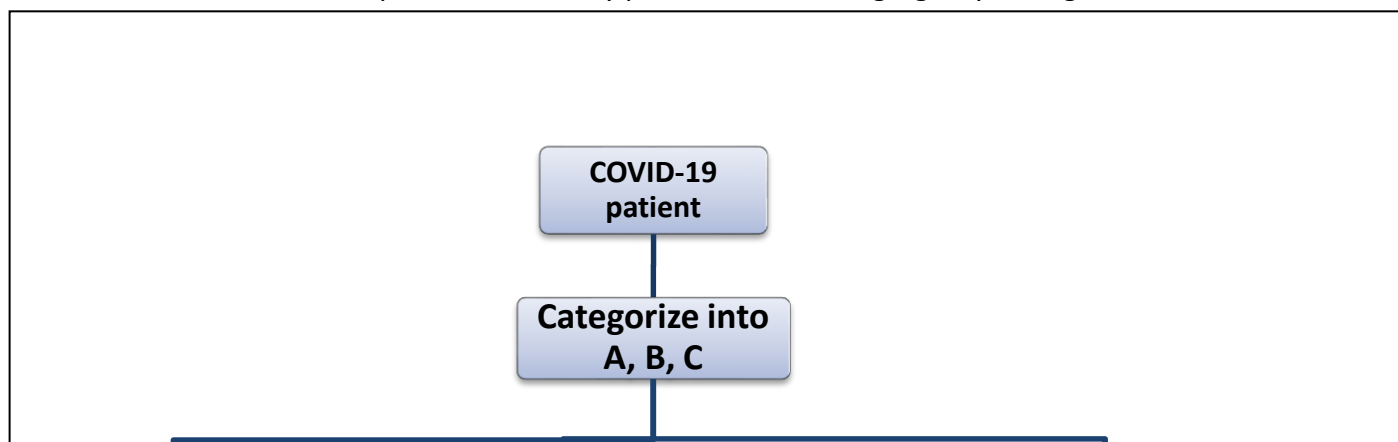
If **CAT C** patient progresses to ARDS/MODS while on HCQS/Chloroquine plus Azithromycin, addition of Lopinavir/Ritonavir may be considered in case of progressive worsening as Remdesivir is not available in India. In that case Azithromycin is to be stopped. QTc is to be monitored very frequently. This combination is to be used on a compassionate ground after taking informed consent explaining the possibility of life threatening QTc prolongation and cardiac arrhythmias.

FOR THOSE WITH EVIDENCE OF CYTOKINE RELEASE SYNDROME [CRS]

GRADE	CLINICAL ASSESSMENT	TREATMENT
Grade 1	Mild reaction: low grade fever, No oxygen requirement or need for IVF	No treatment
Grade 2	Moderate reaction: <ul style="list-style-type: none"> - High grade fever (>103F), need for IVF (not hypotension), mild oxygen requirement(<6L/min) - Grade 2 AKI - Grade 3 LFT(Raised liver enzymes & S Bilirubin≥2.5gm/dl) 	Send for serum IL-6, If not available, use CRP as a surrogate marker
Grade 3	Severe reaction: <ul style="list-style-type: none"> - Rapidly worsening respiratory status with radiographic infiltrates and SpO2 ≤ 93% in room air or on supplemental oxygen (>6L/min, high flow, BiPAP, CPAP) - Grade 4 Liver function test (raised liver enzymes, S Bilirubin > 2.5gm/dl and INR > 1.5, encephalopathy) - Grade 3 AKI - IVF for resuscitation - Coagulopathy requiring correction with FFP or cryoprecipitate - Low dose vasopressor (Nor adrenaline <0.5mcg/kg/min or Adrenaline < 0.3mcg/kg/min) 	Send for serum IL-6 or CRP, Ferritin Consider Tocilizumab >18 years: 8mg/kg IV (max 400mg) <18 years >30kg: 8mg/kg (max 800mg) IV over 60 mins if no effect can repeat x 2 more doses Q8H apart; If no response, consider low dose corticosteroids especially in case on concomitant septic shock.
Grade 4	Life threatening multi organ dysfunction, hypoxia requiring mechanical ventilation, hypotension requiring high dose vasopressors	Send for serum IL-6 or CRP; consider Tocilizumab as in Grade 3; consider corticosteroids.

For grade 3 / 4 CRS when there is no response to Tocilizumab / availability / tolerance issue

Glucocorticoids may be used for a short period of time – 3-5 days. It is recommended that dose should not exceed the equivalent of Methylprednisolone 1-2mg/kg/day. A larger dose



A	Mild sore throat/ cough/ rhinitis/ diarrhea
B	Fever and/or sever sore throat/ cough OR Category-A plus 2 or more of the following Lung/ heart/ liver/ kidney/ neurological disease/ Hypertension/ hematological disorders/ uncontrolled diabetes/ cancer/ HIV-AIDS On long term steroids Pregnant lady Age- more than 60 years OR Cardiovascular disease
C	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.

Contraindications to chloroquine/ HCQS

- QTc > 500msec
- Porphyria
- Myasthenia gravis
- Retinal pathology
- Epilepsy

Pregnancy is NOT a contraindication

If Baseline QT is prolonged – Monitor ECG

For Protease inhibitors

Assess for drug – drug interactions
(including with calcineurin inhibitors)
before starting.

Gastrointestinal intolerance may be seen
Monitor liver function tests while on
therapy.

Discontinue these agents upon discharge
regardless of duration, unless previously
used as maintenance medications for
another indication.

If CAT C progresses to ARDS/ MODS on HCQ/
Chloroquine plus Azithromycin, addition of
Lopinavir/ Ritonavir may be considered

In Children: HCQs 6.5mg/kg/dose BD, day 1 followed by 3.25mg/kg/dose PO BD X 4 days

Azithromycin: 10mg/kg (max 500mg) day 1, followed by 5mg/kg/day on days 2 to 5

Lopinavir/Ritonavir(based on lopinavir component): 14 days to 6 months: 16mg/kg PO BD, <15kg:
12mg/kg PO, 15-25 kg: 200mg-50mg PO BD, 26-35 kg:300mg-75mg PO BD, >35kg: 400mg-100mg PO BD

The [National Task Force](#) for COVID-19 constituted by ICMR recommends the use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection for high risk population.

1. Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19
2. Asymptomatic household contacts of laboratory confirmed cases

DOSE

1. Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: 400mg once weekly for next 7 weeks: to be taken with meals.
2. Asymptomatic household contacts of laboratory confirmed cases: 400mg twice day on Day 1, followed by 400 mg once weekly for next 3 weeks, to be taken with meals.

Exclusion/contraindication

1. Drug is not recommended for prophylaxis in children under 15 years of age.
2. Drug is contraindicated in persons with retinopathy, hypersensitivity to HCQS or 4-aminoquinoline compounds

References

1. Massachusetts General Hospital COVID-19 Treatment Guidance
2. Interim Clinical Guidance for Patients Suspected Of/Confirmed with COVID-19 in Belgium 19 March 2020
3. COVID 19 Management protocol, All India Institute of Medical Sciences, New Delhi
4. Novel Corona Virus Pneumonia diagnosis and treatment scheme for severe and critical cases – COVID 19 Medical care team Central Directive Group of China 13 March 2020
5. Diagnosis and treatment protocol for Novel Corona Virus Pneumonia trial version 7, National health commission China March 3, 2020

AVAILABLE EVIDENCE ON THE USE OF TOCILIZUMAB IN COVID-19

Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody against IL-6 receptor

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

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

Dose recommended for CRS:

- >18 years: 8mg/kg IV (400mg)
- <18 years
 - <30 kg: 12mg/kg IV over 60 minutes
 - >30 kg: 8mg/kg (max 800mg) IV over 60 minutes

The total Tocilizumab dose should not exceed 800mg

If no effect can repeat x 2 more doses Q8H apart;

If no response, consider low dose corticosteroids especially in case of concomitant septic shock can be given as an intravenous infusion in normal saline over 1 hour. Up to 3 additional doses can be administered with at least 8 hr interval between consecutive doses.

Evidence for Tocilizumab in COVID-19

Xu et al reported their experience with Tocilizumab in patients with severe or critical COVID-19 infection. The diagnosis of severity was defined if any of the following conditions was met:

1. Respiratory Rate \geq 30 breaths/min
2. SpO₂ \leq 93% while breathing room air
3. PaO₂/FiO₂ \leq 300mmHg

A critical case was diagnosed if any of:

1. Respiratory failure requiring mechanical ventilation
2. Shock
3. Combined with organ failure, need to be admitted to ICU

The study included 21 patients who received standard therapy including lopinavir, methylprednisolone, other symptom relievers and oxygen therapy along with Tocilizumab. The dose of Tocilizumab used was 400mg single intravenous infusion. 19 patients were discharged from hospital, while 2 were improving in hospital at the time of reporting. The authors also reported that symptoms, hypoxigenemia, and CT opacity changes were improved immediately after the treatment with Tocilizumab in most of the patients.

Ongoing Clinical Trials:

Tocilizumab in COVID-19 Pneumonia (TOCIVID-19) (TOCIVID-19)

This is a multi-center, single-arm, open-label, phase 2 study in severe COVID-19 infection. All the patients enrolled are treated with Tocilizumab. One month mortality rate is the primary end point. Participants will receive 2 doses of Tocilizumab 8mg/kg (up to a maximum of 800mg/dose), with an interval of 12 hours. Primary outcome measurement: 1 month mortality.

Guidelines and recommendations:

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

Tocilizumab: 8mg/kg (maximum 800mg/dose), single dose intravenously (1hour infusion);

Tocilizumab administration should be guided by the presence of 1 or more of the following selection criteria:

PaO₂/FiO₂ ratio < 300

Rapid worsening of respiratory gas exchange with or without availability of non-invasive or invasive ventilation

IL-6 levels > 40pg/ml (if not available, see D-Dimer levels > 1000ng/ml)

Therapeutic Schedule:

Two administrations (each 8 mg/kg, maximum 800mg). 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 reaction, liver test dysfunction, kidney injury, IVF foe resuscitation, low dose vasopressor, supplemental oxygen (high flow, BiPAP, CPAP)
Grade 4	Life threatening, mechanical ventilation, high dose vasopressor

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:

1. COVID-19: consider cytokine storm syndromes and immunosuppression - the Lancet [Internet]. [cited 2020 Mar 21] Available from: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30628-0/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext)
2. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China- PubMed – NCBI [Internet]. [cited 2020 Mar 21]. Available from : <https://www.ncbi.nlm.nih.gov/pubmed/32125452>
3. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. PubMed – NCBI [Internet]. [cited 2020 Mar 21]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed?term=27913530>
4. ACTEMRA (Tocilizumab) injection. Drug monograph
5. Xu et al Effective Treatment of Severe COVID-19 Patients with Tocilizumab. China Xiv:202003.00026v1

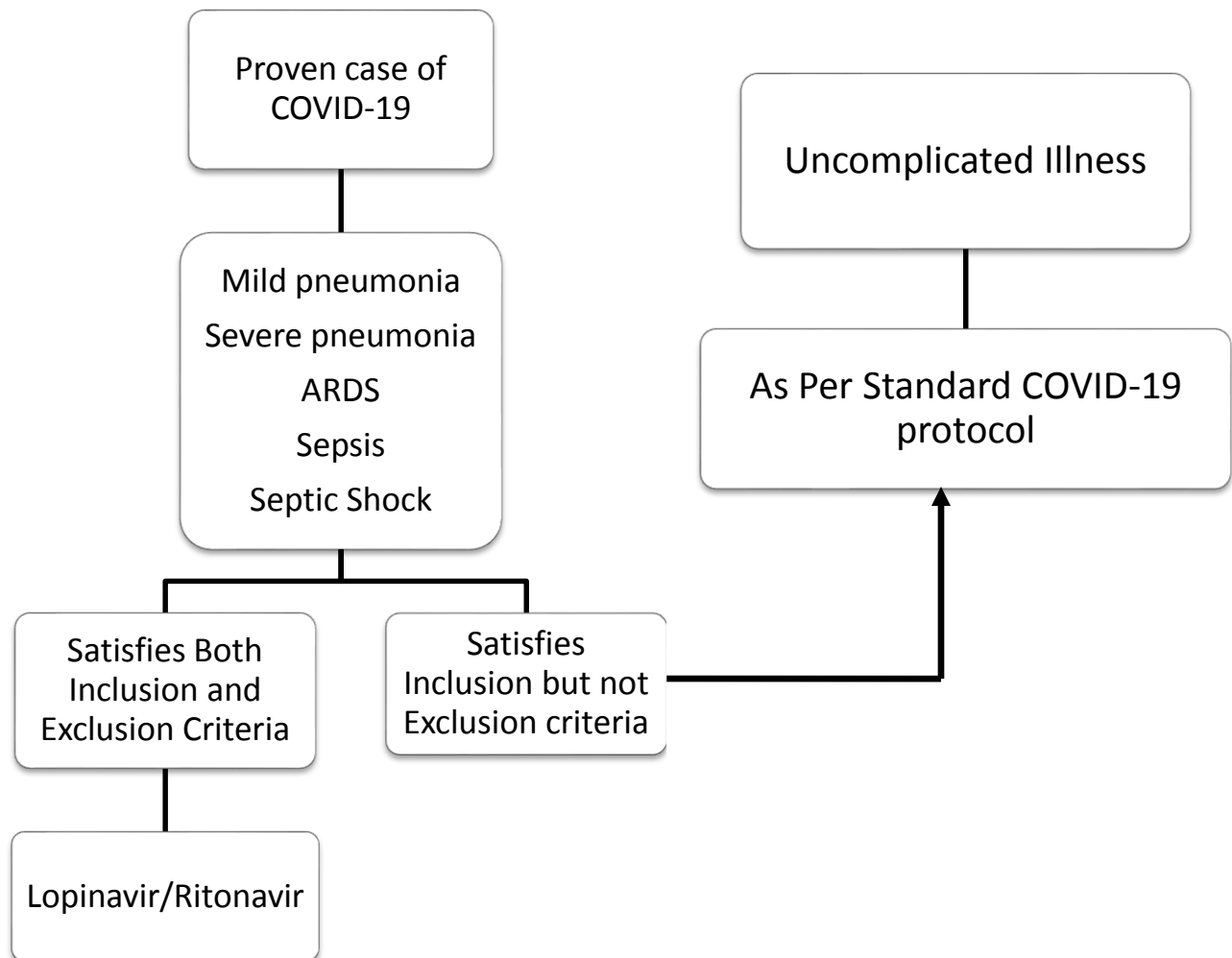
CRITERIA FOR USE OF LOPINAVIR/RITONAVIR IN SYMPTOMATIC PATIENT

- >18 years of age
- Lab confirmatory Covid-19 infection
- Patient with mild and severe pneumonia, ARDS, sepsis and septic shock.
- Informed consent
- Clearance from medical board constituted for Covid-19
- If <18 years clearance from State Medical Board

EXCLUSION CRITERIA

- Asymptomatic individual with covid-19 infection
- Known allergic to Lopinavir/Ritonavir
- Hepatic impairment
- Use of medication that are contraindicated (Astemizole, Terfenadine, Cisapride, Ergot derivatives, Sildenafil, Midazolam, Triazolam, Lovastatin , Simvastatin, Pimozide & Fluticasone propionate)
- K/C/O HIV infection under protease inhibitors
- Documented CLD

ALGORITHM FOR CASE MANAGEMENT



DOSAGE OF LOPINAVIR-RITONAVIR

- ADULTS-Lopinavir/Ritonavir 200mg/50mg 2 tabs every 12 hr for 14 days for 7 days after becoming asymptomatic whichever is earlier.
- For patients unable to take medicines orally ,400 mg Lopinavir/100 mg Ritonavir 5 ml suspension every 12 hrs for 14 days or for 7 days after becoming asymptomatic whichever is earlier, via a nasogastric tube
- Administer, with caution among persons receiving Rifampicin, Ketoconazole, Ethylene estradiol.

LABORATORY INVESTIGATIONS

- Haemogram
- LFT, KFT
- HbA1c and blood sugar
- RT PCR for COVID19
- Investigation for any documented chronic morbidity

Lab sample collection (other than investigations for routine clinical monitoring)

- Blood sample every 48 hrs –for PT/INR,LFT,KFT and serum amylase (to monitor drug induced adverse events)

Frequency and duration of monitoring

- Daily monitoring until discharge from hospital.
- To be discharged based on state protocol in concurrence with the opinion of Institutional medical board (IMB).

ADVERSE EFFECTS OF LOPINAVIR - RITONAVIR

- Acute pancreatitis(defined as having:
 - a) Abdominal pain
 - b) Serum amylase 3 times greater than the upper limit of normal)
- Elevation of ALT to more than 5 fold upper limit of normal.
- Anaphylaxis
- Bleeding diathesis (INR >3 without anticoagulant therapy)
- Diarrhea

ROLES AND RESPONSIBILITIES OF TREATING INSTITUTIONS

- It is responsible for patient management.
- Prior to initiating treatment with Lopinavir/Ritonavir, the IMB will be responsible for obtaining written Informed Consent in the structured format.
- Pt not consenting to receive Lopinavir/Ritonavir will continue to be monitored & treated as per protocol with provision of standard care.
- Case report forms to be filled by treating physician and submitted to IMB

ROLES AND RESPONSIBILITIES OF INSTITUTIONAL MEDICAL BOARD (IMB)

- To decide whether pt with confirmed novel corona virus infection satisfies the criteria to be initiated on lopinavir/Ritonavir.
- To assess the pts who have been initiated on lopinavir/Ritonavir daily.
- To ensure that the case report form is filled properly.
- If pt with high risk contact case of nCoV, presents with ARDS or sepsis, the need for initiation of lopinavir/Ritonavir should be assessed by IMB before referring to State Medical Board.

ROLES AND RESPONSIBILITIES OF STATE MEDICAL BOARD (SMB)

1. If pt with high risk contact of confirmed case of nCoV with ARDS or sepsis, the need for initiation of Lopinavir/Ritonavir should be assessed by SMB and directive should be given to the concerned IMB
2. Any clarification with regard to use of Lopinavir/Ritonavir should be addressed by SMB
3. Treatment decision regarding use of Lopinavir/Ritonavir in confirmed nCoV cases in pt <18 years should be addressed by SMB.

CASE DEFINITION OF CLINICAL SYNDROMES

TERM	DEFINITION
Mild Pneumonia	<p>Patients with pneumonia and no sign of severe pneumonia.</p> <p>Child with non severe pneumonia has cough or difficulty breathing + fast breathing (in breaths/min) ;< 2 months: >=60; 2 –11 months >=50; 1-5 years >=40 and no signs of severe pneumonia.</p>
Severe Pneumonia	<p><u>Adolescent or adult</u>; fever or suspected respiratory infection, plus one of RR> 30 breaths/min, severe respiratory distress or SpO2<90% on room air.</p> <p><u>Child</u> with cough or difficulty in breathing ,plus at least 1 of the following: central cyanosis or SpO2 <90% ;severe respiratory distress (eg grunting ,very severe chest indrawing) ;signs of pneumonia with a general danger sign ; inability to breast feed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest indrawing, fast breathing.</p> <p>The diagnosis is clinical; chest imaging can exclude complications.</p>
Acute Respiratory Distress Syndrome	<p>Onset: new or worsening respiratory symptoms within 1 week of known clinical insult.</p> <p>Chest imaging (radiography, CT scan or lung USG); BL opacities, not fully explained by effusions, lobar or lung collapse or nodules.</p> <p>Origin of edema; respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (eg ECHO) to exclude hydrostatic cause of edema if no risk factor present.</p> <p>Oxygenation (adults);</p> <ul style="list-style-type: none"> • Mild ARDS 200mmhg ,PaO2/FiO2 <=300 mmhg (with PEEP or CPAP >= 5mmhg H2O, 7 or non ventilated 8) • Moderate ARDS ;100 mmhg <PaO2/FiO2 <200mmhg with PEEP >=5mmhg,7 or non ventilated 8) • Severe ARDS PaO2/Fio2 <=100mmhg with PEEP >=5 mmhg ,7 or non ventilated 8) • When PaO2 is not available ,Spo2/FiO2<= 315 suggest ARDS (including in non ventilated pt) <p>Oxygenation children; OI =Oxygenation Index and OSI Oxygenation index using O2)</p> <ul style="list-style-type: none"> • Bi-level NIV or CPAP >=5 cm H2O via full face mask: PaO2 /FiO2 <=300 mmhg or SpO2 /FiO2 <= 264 • Mild ARDS (invasively ventilated) 4<=OI<8 or 5<= OSI<7.5 • Moderate ARDS(invasively ventilated): 8<=OI < 16 or 7.5<= OSI ,12.3 <p>Severe ARDS(invasively ventilated)OI>=16 or OSI>=12.5</p>

TERM	DEFINITION
Sepsis	<p>Adults: life threatening organ dysfunction caused by a dysregulated host response or proven infection, with organ dysfunction. Signs of organ dysfunctions include: altered mental status, difficulty or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low BP, skin mottling or lab evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia.</p> <p>Children: suspected or proven infection and ≥ 2 SIRS criteria of which one must be abnormal temp or WBC count.</p>
Septic Shock	<p>Adults: persisting hypotension despite volume resuscitation ,requiring vasopressors to maintain MAP ≥ 65 mmhg and serum lactate level >2 mmol/L</p> <p>Children; any hypotension (SBP 2 SD below normal range) or 2-3 of the following :altered mental state ;tachycardia or bradycardia (HR 160 bpm in infants and HR 150 bpm in children);prolonged capillary refill (>2 sec) or warm vasodilatation with bounding pulses; tachypnea ;mottled skin or petechial or purpuric rash ;increased lactate; oliguria ;hyperthermia or hypothermia.</p>
Reference	<p>Clinical Management of SARI when N COVID 19 infection is suspected: Interim Guidance by WHO Jan 28 2020</p>

INFORMED CONSENT FORM FOR COMPASSIONATE USE OF LOPINAVIR-RITONAVIR FOR COVID-19 VIRAL INFECTION

Institutional Medical board has informed me that I/my relative has been diagnosed with SARS-CoV-2 infection. They have clearly explained to me that there is no effective and approved medication against COVID-19 infection. They have explained to me in detail that there is some scientific evidence regarding the effectiveness of using Lopinavir-Ritonavir for Corona virus infection like SARS in the past. They have also explained to me that at present a clinical trial is going on in China to ascertain the efficacy of Lopinavir-Ritonavir in people affected by COVID-19. They have explained to me that lopinavir-Ritonavir has been used in treatment of HIV even in children for more than 10 years in India with an acceptable adverse effect profile.

The team of doctors informed me that I have developed pneumonia due to COVID-19, I might benefit by the restricted compassionate use of Lopinavir-Ritonavir. They have clearly explained to me that Lopinavir-Ritonavir has not been approved for the definitive treatment of COVID-19 they have explained to me in detail that as there are no approved anti-viral drugs for COVID-19 and there is a risk of progression to acute respiratory distress syndrome, Lopinavir-Ritonavir may be used. They have explained to me about the probable side effects of Lopinavir-Ritonavir like diarrhea, hypersensitivity, pancreatitis, gastritis and hepatitis. They have made it clear that the standard treatment for COVID-19 infection will be continued irrespective of my decision regarding the compassionate use of Lopinavir-Ritonavir. Knowing that this drug is not approved medication for the treatment of novel corona virus infection, I fully agree to the restricted public health emergency use of this drug for the treatment of my novel Corona virus infection.

Name:

Relation:

Signature:

Institutional Medical Board Members

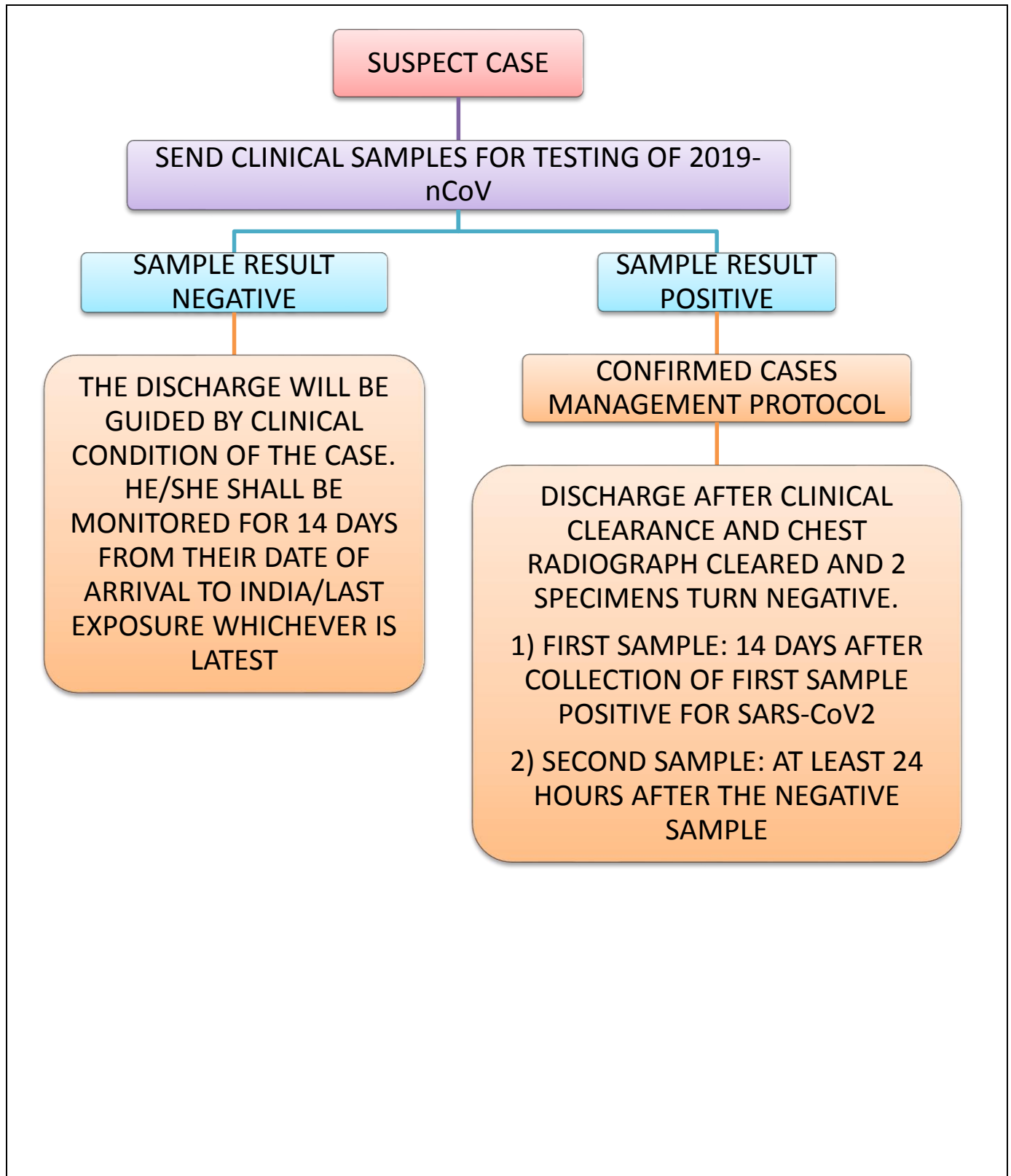
Name

Signature

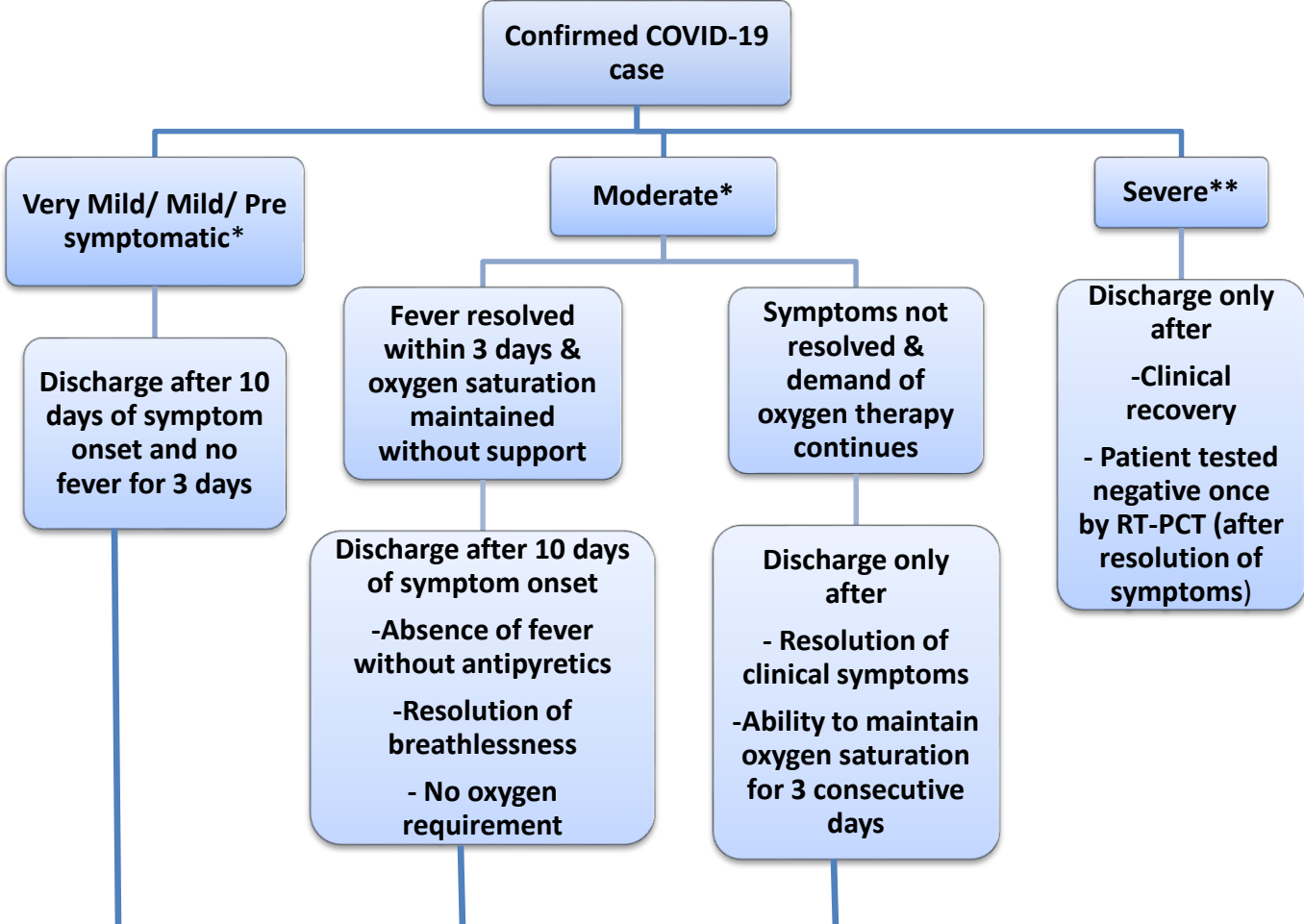
STNM TREATMENT PROTOCOL

GRP	CRITERIA	INVESTIGATIONS	WARD	TREATMENT	SWAB TEST TIMING/ DAY	REMARKS
A	ASYMPTOMATIC	HEMOGRAM	FLU WARD	CAP OSELTAMAVIR (75 MG) FOR 5 DAYS + TAB AZITHROMYCIN 500 MG OD FOR 5 DAYS	0,7,14	BASELINE ECG FOR QTc
B	ASYMPTOMATIC BUT COVID POSITIVE	HEMOGRAM	ISOLATION WARD	SAME AS ABOVE	0,7,14	SAME AS ABOVE
C	SYMPTOMATIC/ URTI WITHOUT COMORBIDITY, COVID POSITIVE 3 OUT OF 4 TO BE PRESENT <ul style="list-style-type: none"> • FEVER • DRY COUGH • SOB • MYALGIA 	CBC,LFT,ECG, CXR PA, NP SWAB FOR COVID	SUSPECT COVID WARD	SAME AS ABOVE + TAB HCQ (400 MG) BD IN DAY 1 AND TAB HCQ (200 MG)FROM DAY 2-5	0, 7, 14	SAME AS ABOVE
D	SYMPTOMATIC/URTI WITH CO MORBIDITY,COVID POSITIVE <ul style="list-style-type: none"> • >60 YEARS • DM • HTN/IHD • COPD/CHR LUNG DISEASE • IMMUNOCOMPROMISED STATE • IMMUNOSUPPRESSIVE DRUGS • CKD 	CBC, LFT, KFT,RBS,SERUM AMYLASE DAILY SERUM ELECTROLYTE,CPKMB, PT INR, CXR PA,ECG, 2D ECHO	ISOLATION WARD	SAME GROUP C + TAB LOPINAVIR/RITONAVIR 200MG +50 MG 2 TABS BD FOR 5 DAYS	0, 7, 14	BASELINE ECG+ DO NOT COMBINE HCQ WITH LOPINAVIR IN VIEW OF DRUG INTERACTION IF PT IS SYMPTOMATIC AT DAY 5 ALSO CONTINUE THERAPY FOR NEXT 5 DAYS THUS FOR 10 DAYS
E	SARI WITHOUT RESPIRATORY FAILURE COVID POSITIVE	CBC ,RBS,LFT,KFT,CXR PA ,ECG,CT THORAX	ISOLATION WARD OR ICU	TAB OSELTAMAVIR 150 BD FOR 5 DAYS + TAB AZITHRO 500MG OD 5DAYS+ TAB HCQ 400MG BD ON DAY 1 AND TAB HCQ 200 MG FROM DAY 2-5 OR TAB LOPINAVIR/RITONAVIR 200/50 2 TAB BD 14 DAYS ANTIBIOTICS INJECTABLES	0, 3, 9, 14	CONSIDER INJ TOCILIZUMAB 60 MG /KG OVER 60 MIN MAX 400 MG ALLOWED IF FIRST DOSE IS NOT ENOUGH REPEAT DOSE AFTER 12 HRS (NOT MORE THAN 2 DOSES)

DISCHARGE POLICY OF 2019-nCoV CASE: OLD



REVISED DISCHARGE POLICY BY MOHFW



NO RT-PCR TEST REQUIRED BEFORE DISCHARGE

Patient to be isolated at home for next 7 days as per guidelines

Clinical categorization of patients as per guidelines

**including immunocompromised (HIV patients, transplant recipients, malignancy)

OUR LACUNAE

- Lopinavir/ Ritonavir (200/50mg) Tablets and Syrup
- Injection Tocilizumab
- Injection Azithromycin
- Remdesivir: not available in India. Third stage clinical trial on
- Need to procure kits for D - Dimer, Ferritin, Procalcitonin
- Anti platelets, Vitamin D, Chelating agents to be added

Dr. Passang Dorjee Phempunadikpa
PCC cum Medical Superintendent
STNM Hospital

Signature

Dr. Namgay Shenga
Additional Medical Superintendent 1
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Dr. Yudok Bhutia
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