Nature of Evolution of Zoonotic Virus, Treatment of Covid-19 Patient and Surgery Protocols: A Study

Dr. Sudarshan Sen[1]
Dr. Ahsan Ahmed[2]
Dr. Amaresh Banerjee[3]
Dr. Viswanath Mahato[4]

ABSTRACT:

Corona virus disease (COVID-19) represents the potentially fatal disease of great global public health concern. Large numbers of infected people were exposed to the wet animal market of Wuhan City, China & this fact suggested that this is likely to be the zoonotic origin of Covid-19. Person to person transmission of this infection created the urgency of isolation of patient who underwent subsequently a variety of treatments. Extensive measures were undertaken to put an end to person to person transmission of Covid-19 infection in an attempt to control current outbreak. We should provide utmost attention & sincere endeavor to protect & minimize transmission in susceptible populations including elderly people, children & health care providers. Some symptoms, epidemiology, pathogenesis, complications, treatment & surgery protocols in COVID-19 era have been highlighted in this article. It is also confusing, because in a zoonotic virus evolution is an ongoing process & this will produce bizarre & different symptoms in different patients with varying severity & infectivity & we should be prepared for 'what next' ! Recurrent antigenic changes in the virus are to be taken care with to find out definite medicine & preventive vaccine.

Keywords*: COVID-19 , WHO, China, Zoonotic, SARS COV-2, MERS COV (2012-2014), Signs, Symptoms, Dyspnea, Cough, Chest X-ray, Cytokine Storm, Dexamethasone, Solumedrol, Oximeter, Bronchiectasis, Hydroxychloroquine, Tocilizumab, Hypercoagulability, Aminoglycosides, Immunomodulators, Immunocompromised, Surgery in pandemic era, Priority Level, Elective patients, Acute patients ,Pneumocytes, ACE 2 Receptors, Antibodies.*

Abbreviations used *: **ACE2 Receptors** = Angiotensin Converting Enzyme 2 Receptor; **CD** = Cluster of Differentiation; **COVID-19** = Corona Virus Disease 2019; **CT** = Computer Tomography; **ICMR** = Indian Council Of Medical Research; **MERS COV** (2012-2014) = Middle East Respiratory Syndrome Corona Virus 2012-2014; **N95** = Not resistant to Oil filters 95 % of airborne particle; **PPE** = Personal Protective Equipments; **SARS –COV-**2 = Severe Acute Respiratory Syndrome - Corona Virus-2; **WHO** = World Health Organization.*

[1]*Assistant Professor, Department of Surgery, KPC Medical College & Hospital; Kolkata*
[2]*Assistant Professor, Dept. of Anesthesiology, Intensivist and ICU In-charge, KPC Medical College & Hospital; Kolkata*
[3]*Assistant Professor, Department of Surgery, KPC Medical College & Hospital.*
[4]*Interne; Department of Surgery, KPC Medical College & Hospital*

1. INTRODUCTION:

In the first week of July 2020, our country reported a huge spike of 22,771 new corona virus cases in 24 hours along with 613 fatalities. On July 5th number of recoveries were 4, 09,083 with 19,000 deaths. This pandemic is spreading fast & recorded positive cases in India reached 6, 73165 as on 5.07.2020.

Covid patients' admission was also increasing in our hospital. Up to first week of July total patients were 590, 431 patients were discharged with 3 deaths. 56 patients were under treatment. At the end of July total admission was 844, 712 patients discharged with 3 more deaths, total death was 6 out of 844. 6 patients required ventilation of which 4 could be revived.

By the time we all know that covid-19 disease created massive public health concern. WHO has already declared public health emergency. Phylogenetic analysis proved Covid 19 to be a potentially zoonotic virus which must have evolutionary development & diversification.[1]

Covid-19 patients may present with intestinal symptoms like diarrhea, pain in abdomen in addition to respiratory symptoms, ultimately culminating in respiratory distress with rapid fall of SPO2 as pulmonary involvement increases in severity. On the other hand MERS-COV or SARS-COV2 patient had diarrhea in low percentage of cases.[2]

By this time we all know that source of both SARS COV-2 of 2002 & and COVID-19 of December'19 is China's wet animal market. First case of an atypical pneumonia emerged in Guangdong Province (China) in late 2002.[3] But it was in February 2003 WHO received reports from China of a new respiratory illness outbreak in Guangdong Province. A novel virus was isolated from patients' lung & sputa & cultivated on monkey kidney cell line. It was proved that this was a previously unrecognized corona virus. This epidemic was officially controlled by July 2003. WHO reported more than 8000 cases with more than 800 deaths worldwide. Epidemic in Middle East countries in 2012-2014 was due to MERS-COV.[4] Now covid-19 of December'19 was traced back to a wet market in Wuhan, China which caused severe respiratory illness & death & WHO was in utter darkness till the end of January 2020, when severe damage was already

[1] (WHO Timeline - Covid-19 2020) World health Organization - WHO Timeline - Covid-19 2020; Retrieved on 12th May, 2020- https://www.who.int

[2] SARS-COV-2 & COVID-19 –Difference ? https://www.cleanlink.com

[3] C.Clai, T-P Shih, W.-C.KO, H.-J.Tang, P.-R.H Sueh severe acute respiratory syndrome Corona Virus-2 (SARS-COV-2) & corona virus disease-2019 (COVID-19) : The epidemic & the challenges. Int J Antimicrobe Agent (2020) Article 105924,2020/02/17 Article download PDF, Google Scholar

[4] Arabi YM, Balkhy HH, Hayden FG, et al – Middle East Respiratory Syndrome. NEJMsr1408795PubMedGoogleScholarCrossref.

done. WHO was informed first by a pathologist from Thailand. Recurrent antigenic changes in this virus has also been reported which requires detection.

2. DISCUSSION :

Corona viruses infect many species of animals including humans. Described for more than half a century, isolation of the prototype murine corona virus strain JHM reported in 1949. Molecular mechanisms of replication & pathogenesis of several corona viruses have been categorically studied since 1970s. By now we know animal viruses' i.e. Porcine Transmissible Gastro Enteritis Virus (TGEV), Bovine Corona Virus (BCOV) & avian Infectious Bronchitis Viruses (IBV).

Data gathered from animal corona viruses helps in understanding human viruses' infection both by SARS COV-2 & COVID-19.

i) We can know short summary of the replication cycle of corona viruses in cell culture.
ii) We can develop & observe application of reverse genetic systems.
iii) Role of corona virus proteins in replication & pathogenesis.
iv) To develop animal models for vaccine development & anti-viral therapies.

The origin of SARS Corona Virus (SARS-COV) poses interesting questions about Corona virus evolution & species specificity. Since the SARS epidemic, two new human respiratory corona viruses have been described.[2]

The name 'Corona Virus' was coined in 1968 from the corona like or crown like architecture observed for these viruses via electron microscope. Corona viruses are divided into 3 genera (I to III) based on serological cross reactivity.[5]

About 19 out of 20 patients with corona virus recover without being admitted to Hospital. Of those who are admitted most also recover from the illness but some may need Oxygen (O2) or Mechanical Ventilation. These are the high risk patients where steroid appears to help. High index of suspicion for elderly or young with co morbidities may help exposed person from deteriorating. Pulse oximeter is a must; it may mark out latent hypoxia (Silent Hypoxia) before severe respiratory distress sets in.[6] A chest x-ray (digital) is mandatory. Pulmonary CT should be done in moderate to severe respiratory difficulty. [7]

[5] Naming of COVID-19; https://www.who.int

[6] Zhou F, Yut, Dur-clinical course & risk factor for mortality of adult in patients with Covid-19 in Wuhan, China : a retrospective cohort study. Lancet 2020; 395:1054-62.

[7] Can Assoc Radiol J 2020 : 846537 120916419.doi:10.1177/0846537120916419

2.1 Symptoms and Signs in Infected Patients :

Covid-19 patients with severe diseases may manifest features like Stroke.[8] Patients presenting with neurologic manifestations during pandemic of COVID-19, we should consider SARS-COVID-2 infection as differential diagnosis. Patient having no other symptoms & fever may complain profound weakness, severe headache, loss of taste sensation & olfaction. [9][10]

Table No -1 : Systemic & Respiratory signs & symptoms in infected patients

Systemic Disorders	Respiratory Disorders [11]
▪ Fever ▪ Cough ▪ Fatigue ▪ Sputum production ▪ Headache ▪ Hemoptysis ▪ Acute cardiac injury ▪ Hypoxemia ▪ Dyspnea ▪ Lymphopenia ▪ Diarrhea	▪ Rhinorrhea ▪ Sneezing ▪ Sore throat ▪ Pneumonia ▪ Acute Respiratory Distress Syndrome

A digital Chest X-ray must be done on admission. Some of the cases may show an infiltrate in the upper lobe of the lung, which should immediately alert the clinician. There are patient in whom increasing dyspnea with hypoxemia will set in without oxygen &respiratory support. These are the high risk patients where steroid should be added.[12]

A cheap & widely available drug can help to save the lives of seriously ill patients with corona virus. The low dose steroid treatment, Dexamethasone[13] is a breakthrough. In our patients with respiratory difficulty we used Solumedrol in a dose of 0.5-1 mg/kg/day in moderately

[8] Avula, Akshay et al - Covid-19 presenting as Stroke. "Brain, behavior, & immunity, S0889-1591(20)30685-1.28 Apr.2020, doi: 10.1016/j.bbi.2020.04.077

[9] Giacomelli A, Pezzati L, Couti Fetal-self reported olfactory & taste disorders in SARS-COV-2 patients: a cross sectional Study. Clininfect Dis.2020, published online March 26 DOI: 10.1093\cid\ciaa330

[10] JIMA volume 64 (RNI) Number 05 May 2020.Kolkata.

[11] Xydakis, Michaels et al – smell & taste dysfunction in patients with Covid-19. The Lancet Infectious Diseases, Volume 0, Issue 0, DOI : https://doi.org/10.1016/S1473-3099(20)30293-0 (20)30293-0

[12] Nasir MU. Roberts J. Muller NL – The Role of Emergency Radiology in Covid-19 : From Preparedness to Diagnosis.

[13] Use of steroids in COVID-19; https://www.ncbi.nlm.nih.gov

severe cases. A trial led by a team of Oxford University using Dexamethasone claimed steroid cut the risk of death from 40 % to 28 % for patients on ventilators. For patients in need of Oxygen, Dexamethasone cut the risk of death from 25 % to 20 %. In their trial 2000 hospital patients were given Dexamethasone & compared with more than 4000 that were not. Steroid does not help people with mild symptoms of corona virus.

Diagnosis is based on History, Symptoms, Clinical Signs, Real time PCR, Antibody Tests, Blood examination, CXR, Chest CT. [14]

We have seen sudden severe worsening of apparently stable recovering Covid-19 patient due to sudden severe hypoxemia & respiratory distress syndrome needing ventilator support & perishing within 6-7 hours. Normal lung alveoli quickly being occupied by inflammatory infiltrates causes' ground glass opacity.

This complication maybe due to Cytokine Storm,[15] a maladaptive cytokine release in response to infection & other stimuli. A complex pathogenesis is involved which includes loss of regulatory control of pro-inflammatory cytokine production both at local & systemic levels. Disease progresses rapidly & the mortality is very high. Sudden severe deterioration in some Covid-19 patient is due to excessive & uncontrolled, deregulated cytokine release. SARS-COV-2, MERS-COV & Covid-19 mainly infect Alveolar Epithelial Cells (AEC).

2.2 How to get rid of Storm:

Table No-2 : How to get rid of Storm [16]

1. INF –Lambda – These activates epithelial cells & reduce mononuclear macrophages mediated pro-inflammatory activity of INF –alpha beta. This also inhibits Neutrophil to reach site of inflammation. 2. Corticosteroids therapy (Solumedrol) 3. Intravenous Immunoglobulin 4. IL-6 antagonist	5. TNF blockers 6. IFN- alpha beta inhibitor 7. IL-1 family antagonist 8. Chloroquine 9. Ulinastatin 10. Stem cell therapy 11. Blood purification treatment

[14] ALT, Yang Z, Hou H – Correlation of Chest CT & RT-PCR Testing in Corona Virus Disease 2019 (Covid-19) in China : A report of 1014 cases Radiology 2020 : 200642.doi: 10.1148/radiol.2020200642

[15] B.G. Chousterman, F.K. Swirski, G.F.Weber Cytokine Storm & Sepsis disease Pathogenesis, Seminars Immunopathol, 39 (5) 2017, PP.517-528 2017/07/01 Cross ref. View Record in scopus Google Scholar

[16] The Pathogenesis & treatment of 'Cytokine Storm' in Covid-19 Qingye, Biliwang, Jianhua Mao; https://doc.org/10.1016/J.Jinf 2020.03.037 Journal of Infection, Volume 80, issue 6, June 2020, Page 607-613

Blood examination in severe cases should also include CRP, IL-6, IL-1, D-dimer, Interferon, and Creatinine. Timely control of Cytokine storm in its early stage is the key to success in reducing the mortality in patients with Covid-19.

3. OUR PATIENT TREATMENT :

3.1 Management in General Wards : [17]

i) **Case Definition of Mild Disease : FEVER** >100 F with sore throat, cough, malaise, myalgia, without Shortness of Breath.

ii) **Case Definition of Moderate Disease: FEVER**>100 F with- Cough, Sore Throat, Myalgia, Difficulty in Breathing; and any one of the following-
   a) Respiratory Rate > 24/min,
   b) SpO2 (oxygen saturation) < 95 % in room air
   c) Altered Sensorium - Drowsiness / Confusion / Stupor
   d) Infiltrates on Chest X-ray.
   e) Altered Liver Function Test or Renal Function Test

iii) Case Definition of Severe Disease : Case with Moderate Disease Plus ARDS / Acute Respiratory Failure and/or, Sepsis with Multi-Organ Dysfunction Syndrome and/or, Septic Shock

3.1.2 Management of Mild Cases:

Following parameters should be observed by doctor / sister during daily rounds and recorded thrice daily / on worsening of symptoms.

i) Temperature
ii) SpO2 (By Pulse Oximeter)
iii) Blood Pressure
iv) Sensorium (conscious, drowsy or stupor)
v) Pulse
vi) Respiratory Rate
vii) Urine Output
viii) Chest Examination - Breath sound, crepitations and rhonchi

First seven features may be checked by the on duty sister. First five parameters are essential and must be recorded time to time in each Shift and duly recorded in the Top Sheet.

3.1.3 Investigations for Mild Cases:

[17] Patient management in general wards; https://www.wbhealth.gov.in/uploaded_files/corona/Management_Protoco_for_COVID-19_-_WB_2nd_Edition.pdf

a) **Complete Hemogram**- common abnormalities are Leucopenia with Lymphocytopenia (On Admission and Daily)
b) **X-Ray Chest-** PA (posterior-anterior) view (On admission / every 3rd day/ at worsening of symptoms)
c) **LFT (LIVER FUNCTION TESTS)** - Raised Transaminases, Hyper bilirubinemia (Send on Admission / day 4 / day 7 / on Worsening)
d) **Serum Creatinine** - May be raised (Send on Admission / day 4 / day 7 / on Worsening)
e) **ECG (ELECTROCARDIOGRAM)** - To look for ST-T changes suggestive of Myocarditis changes and to look for QTc
f) Prolongation. Hydroxychloroquine is to be administered cautiously, if QTc is >450 mSecs,
g) And to be avoided if >500 mSecs.(To be done on Admission / on Worsening of symptoms)

3.1.4 Treatment of Mild Cases: Symptomatic Treatment:

i) Rest
ii) Paracetamol for FEVER
iii) Antitussive for COUGH
iv) ORS for DIARRHOEA
v) Metered Dose Inhalers (Asthalin inhaler 2 puffs TDS-THRICE DAILY) for MILD BREATHLESSNESS
vi) Plenty of Fluids Orally
vii) Nutritious Diet
viii) Tab. **Hydroxychloroquine** 400mg BD- TWICE DAILY on Day 1, followed by 400 mg OD- ONCE DAILY for 4 Days (Contraindications for Hydroxychloroquine: Children below 12 years, QTc in ECG >500 mSec, Retinal Pathology, Drug Interactions, Myasthenia Gravis, Porphyria, Epilepsy).

3.1.5 Treatment of Co-morbidities: If there is any like diabetes, hypertension, heart disease etc.

3.2 When to Call Your Consultant for Refer to Higher Facility:

Any patient developing any one of the following:

i) SpO2 < 95% at Room Air
ii) Confusion, Drowsiness
iii) SBP (SYSTOLIC BLOOD PRESSURE) <90 mmHg, DBP (DIASTOLIC BLOOD PRESSURE) <60 mmHg
iv) X-Ray Chest PA- showing bilateral infiltrate / unilateral infiltrate / Ground glass opacity
v) Deranged Liver or Kidney Function
vi) ST-T changes in ECG suggestive of Myocarditis
vii) Exacerbation of Co-morbid Conditions

3.3 When to Discharge:

i) Mild / Very Mild / Pre-symptomatic cases can be discharged after 10 days of Symptom Onset with NO Fever for at least 3 days

ii) Swab testing or Chest X-Ray is not required for discharge

3.4 Follow Up (Must be written in Discharge Certificate):

i) Strict Home Isolation for 7 days after discharge;

ii) Clinical Follow up at 14th day and 28th day;

3.5 Management in ICU : [18]

3.5.1 Case Definition of Moderate Disease:

FEVER>100 F with- Cough, Sore Throat, Myalgia, Difficulty in Breathing; and any one of the following:

a) Respiratory Rate > 24/min,
b) SpO2 < 95 % in room air
c) Altered Sensorium - Drowsiness / Confusion / Stupor
d) Infiltrates on Chest X-ray.
e) Altered Liver Function Test or Renal Function Test

3.5.2 Case Definition of Severe Disease

Case with Moderate Disease Plus ARDS (ACUTE RESPIRATORY DISTRESS SYNDROME) / Acute Respiratory Failure and/or, Sepsis with Multi-Organ Dysfunction Syndrome and/or, Septic Shock.

Table No.1 : ARDS classification of cases in adults & children

ADULTS	CHILDREN
• MILD ARDS : PaO2/FiO2 > 200- <300 mm Hg (with PEEP or CPAP > 5 cm H2O OR non-ventilated) • MODERATE ARDS : PaO2/FiO2 > 100 - < 200 mm Hg (with PEEP > 5 cm H2O, or non-ventilated) • SEVERE ARDS : PaO2/FiO2 < 100 mm Hg (with PEEP > 5 cm H2O, or non-ventilated) When PaO2 is not available, SpO2/FiO2 < 315 mm Hg suggests ARDS (including in non-ventilated patients)	• Bi-PAP or CPAP > 5 cm H2O via full face mask : PaO2/fIo2 < 300 OR SpO2/FiO2 < 264 • Mild ARDS (invasively ventilated) : OI > 4 - <8 OR , OSI > 5 - < 7.5 • Moderate ARDS (invasively ventilated) : OI > 8 - < 16 OR , OSI > 7.5 - < 12.3 • Severe ARDS (invasively ventilated) : OI > 16 OR , OSI > 12.3

OI = OXYGENATION INDEX

OSI = OXYGENATION IDEX using SpO2

[18] Patient management in ICU;
https://www.wbhealth.gov.in/uploaded_files/corona/Management_Protocols_for_COVID-19_-_WB_2nd_Edition.pdf

Table No 2 : SEPSIS , SOFA Score > 2

SEPSIS	SOFA (TOTAL SCORE 0-24)
Life threatening organ dysfunction caused by a dysregulated host response or proven infection.	1. PaO2-FiO2 Ratio (score 0-4) 2. Platelet count (score 0-4) 3. Bilirubin (score 0-4) 4. Glasgow coma scale (score 0-4) 5. MAP & Vasopressor Requirement (score 0-4) 6. Creatinine & / or Urine output (score 0-4)

Sepsis = SOFA > 2 (BASELINE SCORE TO BE ASSUMED AS 0 IF DATA NOT AVAILABLE)

Table No. 3 : Septic Shock

ADULTS	CHILDREN
Persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP > 65 mm Hg & serum lactate level > 2 mmol/l	Any hypotension (SBP 2 SD below normal for age) or ny 2 of the following – 1. Altered mental state 2. Bradycardia or tachycardia (heart rate 160 beats per minute in infants & heart rate 150 beats per minute in children) 3. Prolonged capillary refill (>2 sec or warm vasodilation with bounding pulses 4. Tachypnea 5. Mottled skin or petechial or purpuric rash 6. Increased lactate 7. Oliguria 8. Hyperthermia or hypothermia

3.5.3 Management of Moderate / Severe Cases

Following Parameters Should Be Observed By Doctor / Sister during Daily Rounds and Recorded Thrice Daily / On Worsening of Symptoms-

i) Temperature
ii) SpO2 (By Pulse Oximeter)
iii) Blood Pressure
iv) Sensorium (conscious, drowsy or stupor)
v) Pulse
vi) Respiratory Rate
vii) Urine Output
viii) Chest Examination - Breath sound, crepitations and rhonchi

First seven features may be checked by the On Duty Sister. First five parameters are essential and must be recorded time to time in each shift and duly recorded in the Top Sheet.

3.6 Investigations:

3.6.1 Main Investigations:

Sl. No	Investigation	Descriptions
1	**Complete Hemogram**	common abnormalities are Leucopenia with Lymphocytopenia (On Admission and Daily)
2	**X-Ray Chest**	PA view (On admission / every 3rd day/ at worsening of symptoms)
3	**LFT**	Raised Transaminases, Hyperbilirubinemia (Send on Admission / day 4 / day 7 / on Worsening)
4	**Serum Creatinine**	May be raised (Send on Admission / day 4 / day 7 / on Worsening)
5	**ECG**	To look for ST-T changes suggestive of Myocarditis changes and to look for QTc Prolongation. Hydroxychloroquine is to be administered cautiously, if QTc is >450 mSecs, & to be avoided if >500 mSecs. (To be done on admission / on worsening of symptoms)

3.6.2 Additional Investigations for Moderate / Severe Cases are as Following:

(1) Appropriate Cultures Blood / Urine (On Admission / on Worsening of symptoms)
(2) For Diabetic patients - FBS, PPBS (as appropriate) [Laboratory / Glucometer]
(3) Serum **Ferritin**
(4) **Trop-T** / Quantitative Troponins (When Suggestive)
(5) Procalcitonin (To rule out secondary infection) - May be normal or mildly elevated
(6) CRP
(7) LDH
(8) **D-Dimer** / PT / INR / APTT / Fibrinogen / Platelets (To rule out DIC)
(9) Nasopharyngeal Swab for H1N1 (To rule out Swine Flu)
(10) CT Scan Chest (Non-contrast) - If Chest X ray inconclusive or negative and suspicion is high
(11) USG Chest: Where expertise available, can be used, as it may help sparing CT scan for all

3.7 High Risk Group Patients :

(i) Age > 60 years
(ii) Chronic Lung Diseases
(iii) Chronic Liver Disease
(iv) Chronic Kidney Disease
(v) Hypertension
(vi) Cardiovascular Disease
(vii) Cerebrovascular Disease
(viii) Diabetes
(ix) HIV
(x) Cancers
(xi) On Immunosuppressive drugs

3.8 Investigations to Predict Progression:

Sl. No	Investigation	Descriptions
1	**CBC**	Monitor lymphocyte count. Lymphopenia is a risk factor for progression to severe disease **Neutrophil Lymphocyte Ratio >3.13** is an independent risk factor for severe disease
2	**CRP**	Elevated levels of CRP may be seen in moderate to severe disease.
3	**Liver Function Test**	Raised Transaminases, Hyperbilirubinemia. Acute liver failure in severe cases
4	**Renal Function Test**	Increased Creatinine. Acute Kidney Injury in severe disease
5	**LDH**	Elevated LDH levels seen in moderate to severe disease. Marker of Poor prognosis
6	**CT chest**	**CT chest** showing thickened interlobular and intralobular lines with crazy paving appearance, bronchiectasis with a Ground Glass Opacities, sub pleural bands and architectural distortion, Bilateral Ground Glass Opacities (GGO) without Sub pleural Sparing, with a posterior predominance.
7	**Ferritin**	Markedly elevated Ferritin level predicts a poor outcome in patients with COVID-19
8	**D-Dimer, P-Time, APTT**	(i) D-dimer >1mcg/ml predicts poor prognosis at an early stage. (ii) Increased D-Dimer, P-Time, APTT are markers of DIC/ Hypercoagulability and bad prognosis (iii) Low Molecular Weight Heparin e.g. Enoxaparin 1mg/kg/day Subcutaneously may be (iv) Considered in patients with very high D-dimer levels (> 6 times normal)

3.9 Salient Points in Management:

3.9.1 Oxygen Therapy:

- Administer oxygen to all Severe Acute Respiratory Illness (SARI) patients and to patients with respiratory distress / hypoxemia / shock
- Start with nasal prongs @ 5L/min, or Simple Face Mask / Venturi Mask / Non-Rebreathing
- Mask @ 6-15L/min, as needed
- Titrate for target SpO2 ≥ 95 %
- Target SpO2 after initial stabilization: 90-96%

3.9.2 Initial Fluid Management:

- Conservative fluid strategy if no evidence of shock (0.9% saline / Ringer lactate)
- Cautious IV fluids
- Monitor for worsening of oxygenation during fluid therapy

3.9.3 Specific Drug Therapy for COVID-19:

- **Tab. Hydroxychloroquine** 400mg BD on Day-1, followed by 400 mg OD on Day-2 to Day-5
- **Contraindications for Hydroxychloroquine**: Children below 12 years, QTc in ECG >500 mSec, Retinal Pathology, Drug Interactions, Myasthenia Gravis, Porphyria, Epilepsy.
- If initial QTc >450 mSec, perform basic biochemistry and ECG daily. Avoid Quinolones and Macrolides with Hydroxychloroquine, if possible. Monitor QTc closely if these are needed.

3.9.4 If there is Progressive Worsening of Condition:

i) **Tocilizumab-** May be considered in Moderate / Severe cases, if IL-6 is more than 5 times of the Upper Limit of Normal (ULN). Recommended first dose is 400 mg (4 - 8 mg/kg) in 100 ml NS, over >1 hour. For patients with poor initial efficacy, an additional 400 mg can be repeated after 12 hours. Maximum number of administrations is two times, and maximum single dose is 800 mg. Not recommended in patients with active hepatic disease or hepatic impairment with baseline ALT or AST >1.5 times of ULN.

ii) **Therapeutic Plasma Exchange** May be considered in Moderate / Severe cases, if there is progressive worsening of condition.

3.9.5 Anticoagulation:

Low Molecular Weight Heparin e.g. Enoxaparin 1mg/kg/day, Subcutaneously, in moderate to severe patients with marked elevation of D-dimer level, P-time and APTT, which suggest the presence of DIC or Hypercoagulability, or in patients requiring venous thromboembolism (VTE) prophylaxis, unless there is a contraindication.

3.9.6 Glucocorticoids :

For patients with progressive deterioration of oxygenation indicators, imaging and excessive of body's inflammatory response, glucocorticoids can be used for a short period of time of 3 to 5 days. Dose not to exceed the equivalent of Methylprednisolone 1- 2mg/kg/day.

3.9.7 Empiric Antimicrobials:

(i) To add antimicrobials to all patients as early as possible, preferably within the first hour;

(ii) Broad Spectrum 3rd generation Cephalosporin / PiperacillinTazobactam / Carbapenem / with or without Aminoglycosides may be selected.

(iii) Azithromycin may be added to cover atypical organisms.

(iv) Choose drugs to cover all suspected bacteria and influenza (Oseltamivir when suspected).

(v) Try to send blood cultures before starting antimicrobials; do not delay antimicrobials waiting to send cultures.

(vi) De-escalate or stop based on microbiology results or clinical judgment or Procalcitonin.

3.9.8 Continuation of Chronic Medications:

(i) ACE inhibitor /ARB- Should be continued, if there is no hypotension or any contraindication.

(ii) Statins- To be continued as same dose**.**

(iii) Insulin - To be continued as per blood sugar.

(iv) Immunomodulators - Decisions to be individualized for prednisolone, biologics and others.

3.9.9 Address Comorbidities : Tailor management according to co morbidities.

3.9.10 Monitoring:

- Monitor vital signs, SpO2 and/or PaO2 at regular intervals (every 2 hourly or on worsening).
- Check whether tolerating oxygen therapy → do not delay intubation if worsening.
- If **High Flow Nasal Cannula (HFNC)** is available, it can consider a short trial of HFNC in selected patients under close monitoring on worsening of oxygenation. Decrease flow, if possible, to restrict aerosol generation → do not delay intubation if worsening.
- If HFNC not available, that can consider a short Non-invasive Positive Pressure Ventilation (NIPPV – Nasal Intermittent Positive Pressure Ventilation) trial in selected patients under close monitoring. (Be careful about leaks, as high flow of NIPPV increases aerosol generation. Full face mask / helmet interface preferred) → Do not delay intubation if worsening.
- Airborne precautions must during HFNC / NIPPV / Endotracheal intubation.
- MDI with spacer preferred to nebulizers, if possible.
- CBC / LFT / RFT / portable Chest X-ray / ECG / Lactate / Procalcitonin (every day).
- ABG 6 hourly or more frequently if needed.
- D dimer, LDH, Ferritin on admission and on alternate days.
- Early detection of myocardial involvement by Troponins, NT-proBNP and Echocardiography.
- Other investigations as decided by treating team.

3.9. 11 Aerosol Generating Procedures:

- Intubation, Extubation, Use of T piece or any other open circuit;
- High Flow Nasal Cannula (HFNC), Non-Invasive Positive Pressure Ventilation, Bag Masking;
- Open Suctioning;
- Bronchoscopy, Tracheostomy;
- Cardio-Pulmonary Resuscitation (CPR);
- Nebulisation.

3.10 Management in Critical Care Unit (CCU):

3.10.1 Criteria of Critical Care Unit Admission:

i) Requiring Mechanical Ventilation;
ii) Hypotension Requiring Vasopressor Support;
iii) Worsening Mental Status;
iv) Multi-Organ Dysfunction Syndrome (MODS).

3.10.2 How to Incubate:

(i) Full complement of PPE with face shield;
(ii) Ensure scene safety & check readiness of all essential drugs & equipment prior to procedure;
(iii) Most experienced team member to intubate;
(iv) Complete airway assessment prior to procedure;
(v) Hemodynamic evaluation & optimization, if needed, prior to procedure;
(vi) Use Heat and Moisture Exchanger (HME) filter + Bacterial-viral filter in every oxygenation;
(vii) Interface (Face Mask, Circuit, Endotracheal Tube (ETT), Catheter Mount, Laryngeal Mask Airway (LMA));
(viii) Use closed system suctioning;
(ix) Pre-oxygenation with 100% oxygen;
(x) Rapid sequence intubation using induction agent (Propofol or Etomidate) and muscle relaxant (Succinylcholine or Rocuronium);
(xi) Limit bag mask ventilation unless unavoidable;
(xii) Apply cricoid pressure only in case of ongoing regurgitation;
(xiii) Use video laryngoscope with separate screen, if available;
(xiv) In anticipated difficult airway, anesthesiologist may be called to intubate;
(xv) In unanticipated difficult airway, use LMA and simultaneously call for expert help.

3.10.3 COVID-19 and Cardiac Arrest: Cardiopulmonary Resuscitation:

(i) In the event of a cardiac arrest, cardiopulmonary resuscitation should proceed with all members of the team wearing full PPE and N95 mask.

(ii) Bag-mask ventilation should be avoided (if feasible) and the ventilator can be used instead to deliver a respiratory rate of 10 beats per minute.

(iii) "Crashes" should be avoided by close monitoring and anticipation. Aim for an elective, unhurried intubation.

(iv) Meaningful outcome in refractory critical illness and multiple organ failure is <5%: Assess futility of treatment early.

3.10.4 Discharge Criteria in Moderate / Severe Cases

(1) Moderate cases whose symptoms resolve within 3 days and maintains SpO2 above 95% for next 4 days can be discharged after 10 days of symptom onset if there is absence of fever without Paracetamol, Resolution of breathlessness and No oxygen requirement.

(2) Moderate to severe cases whose fever does not resolve within 3 days and demand of oxygen therapy continues can be discharged only after Resolution of clinical symptoms and ability to maintain oxygen saturation above 95% for 3 consecutive days.

(3) Severe Cases (including Immunocompromised patients, HIV patients, Transplant recipients and Malignancy) can be discharged only after Clinical recovery and the patient's swab test becomes negative once by RT-PCR after resolution of symptoms.

3.10.5 Follow Up:

- Strict Home Isolation for 7 days after discharge *(must be written in discharge advice)*;
- Clinical assessment may be carried out after 14 days & 28 days or as required in between.

4. Surgery in Covid-19 Pandemic Era:

Data are becoming available now to inform surgeons about post operative risks. Major surgery performed in Covid positive patients whether diagnosed peri-operatively or post-operatively have substantial risks. But early reports suggested elective major surgeries might be carried out with acceptable risks in a group of selected patients who were self isolated, swab negative cancer patients where perioperative care took place in Covid cold environment.

Standard practice to create & maintain relatively Covid cold site is either unknown or yet to be precisely defined. We know staffs & patients testing, good bed management, attention to

patient flow is all important. We have two types of patients divided on the basis of potential infection risks.[19]

a) **Elective patients who are** –
   - Isolated for 14 days.
   - Screened by selected questions
   - Tested by throat swab within 72 hours of surgery
   - Undergoing surgery in a Covid cold site.

b) **Acute patient-**
   - Status unknown
   - Potential risk to themselves & others
   - Patients requiring CT Abdomen or Pelvis for diagnostic purposes must also have CT chest, unless reliable & rapid alternative testing methods of same standards are available locally.

We must be strict enough to consider-
- Safety of all health care workers;
- Infection routes;
- Resource priorities ;
- Outcome of the individual patient.

There is rising concern regarding uncontrolled release of pressurized gas in Laparoscopic Surgery & use of electro cautery & other devices in open surgery. Proponents of Laparoscopy during Pandemic highlighted potential risks & the need for risk mitigation strategies. These include the technological protection & enhanced PPE.

Risks of viral infection & dissemination from surgical smoke plume are unknown. A greater amount of carefulness & caution must be needed with all emergency surgeries in terms of safety, diagnosis & requisite treatment choices. Strict, scrupulous continued use of adequate PPE remains essential. As we steer through pandemic era further information must be available in due time & will be incorporated in practice. Minilap & Key hole Surgery with minimal instruments & crowding may be of some benefit in this pandemic era. Patients requiring surgery amidst COVID-19 Pandemic are classified in the following groups. (Royal College of Surgeon's guide). [20]

- **Priority Level 1a Emergency :** Operation is required within 24 hours.
- **Priority Level 1b Urgent :** Operation needed within 72 hours.

[19]The LANCET, volume 395, number-10229, pages-1011-1088, March 28th to April 3rd, 2020

[20] Royal College of Surgeons directive regarding surgical patients; https://www.rcseng.ac.uk

- **Priority Level 2 Surgery :** Can be deferred for up to 4 weeks.
- **Priority level 3 Surgery :** Can be delayed for up to 3 months.
- **Priority Level 4 Surgery :** Can be delayed for more than 3 months.

These time intervals may vary & can result in increased risk of an adverse outcome due to progression or worsening of the condition. But surgeons will have to work with in the resources available in the crisis period.

5. Summary :

- SARS-COV was transferred from Civet cats to humans & MERS-COV (2012-14) from Dromedary Camels.
- Covid-19 is the name given to the type of corona virus identified in December'19 to January'20 & was traced back to a wet market in Wuhan, China.
- Recurrent antigenic changes in the virus caused severe concern & will have to be determined by the scientists throughout the globe.
- Discovery of definite medicine & vaccines for prevention is much waited.
- Prognosis depends on cytokine activation, coagulopathy & virus evading immune reaction.
- We will have to learn why 36 years old Covid infected doctor without co morbidities requires ECMO (Extra Corporeal Membrane Oxygenation) for respiratory distress & dies in spite of all the efforts to save him & 90 years old Covid positive patient comes out of hospital with flying colors.
- We are learning every day & recurrent antigenic change in the evoluting zoonotic virus expected to give us lessons on 'what may come next.'
- Human corona virus is largest RNA virus.
- 4 structural proteins serve different functions.
- Spike proteins helps attachment to host receptors, membrane protein gives shape to the virions, binds to Nucleocapsid. Envelope (E) protein, helps release of virus, responsible in pathogenesis. The Nucleocapsid (N) protein binds viral RNA genome.
- No specific information is there regarding pathogenesis of Covid-19 . There is scope for further research. More information is awaited.
- Chest X-ray is essential in Covid-19 pandemic & worsening clinical situation. During imaging suspected or proven patients (Covid-19) radiologist, technologist should use PPE, facemasks, face shields, gloves, head covers etc. Equipment should be thoroughly cleaned. Chest x-ray should be of high quality. Portable bed side examination may restrict disease spread.
- Covid-19 presents more with lower respiratory tract symptoms & related symptoms.
- New therapeutic & preventive measures will emerge from thorough knowledge of Anatomy & Physiology of virus & its complex interplay with host cells.

- Intensivist managing Covid positive patients with co morbidities like COPD, Sleep Apnea may do better with prone ventilation.
- Covid-19 patients may need Heparin Prophylaxis to guard against thrombotic episodes. Thrombosis may result from Covid infection due to complement activation with deposition of C5b-9 in the endothelium. Virus may itself cause endothelial injury.[21]
- In our country antibody testing was proposed in some cases after 7 days of illness.
- ICMR had proposed a prophylactic course of HCQ for Physicians. 400mg BD on Day 1 followed by 400mg weekly for 7 weeks. Primary contacts in our country are often quarantined at home.
- Pneumocytes 1 lines lung alveoli & Pneumocytes 2 produce surfactants which maintain Lung compliance. Due to preponderance of ACE2 receptors in the Pneumocytes of lung alveoli corona virus also has predilection to Pneumocytes for this reason. In mild to moderate cases of Corona infection inflamed alveoli is full of exudates. There is impairment of gas exchange, lung compliance though remaining normal at this stage, oxygen cannot mix adequately with blood but Carbon dioxide diffuses out. Diffusion Capacity of CO2 being twenty times more than O2. This is why hypoxia occurs at this stage without hypercapnia. As work of breathing is undisturbed, breathlessness does not occur at this stage in spite of hypoxia. This silent hypoxia must be detected in Covid patients. Obviously in late stages fall of surfactants also occurs, lung compliance is reduced & patient develops dyspnea as work of breathing is increased. When Lobar Pneumonia occurs in other instances consolidated lung causes hypoxia. Hypoxemia may cause vasoconstriction in compliant lungs causing dire trouble.
- In our patients mean age was 50 years, majority of patients were more than 50 years old & 70 % were male.

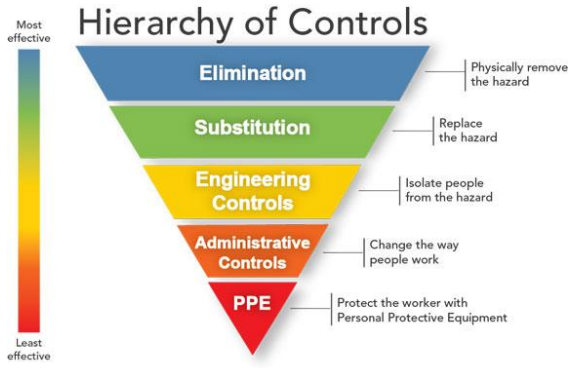

Figure No. 1 : Hierarchy of Controls of Disease

[21] Cuker A, Peyvandi F. Corona virus disease 2019 (Covid-19) : Hypercoagulability up to date [Internet] [Updated 2020 May 11; cited 2020 May 13].Available online from https://www.uptodate.com\contents\Coronavirus-disease-2019-covid-19-hypercoagulability

6. Conclusion :

- It is the beginning of learning, knowledge is yet to be completed.
- Presentation of viral antigenic peptides to antigen presentation cells of the host is of utmost importance in pathogenicity and development of specific immunity.
- IgM is developed as acute phase response and IgG antibody denotes chronic phase response. IgM is detectable within 5-7days and persists for about one week before disappearance. IgG antibodies are specific persisting for years having protective role.
- Severe form of disease with poor prognosis may be indicated by increase in Neutrophil count and Neutrophil : Lymphocyte ratio.
- Cellular immunity is greatly reduced in Covid-19 patients as evidenced by reduction of CD4+ and CD8+T-cells.
- Covid-19 virus is very fond of ACE2 receptors present in Lung Pneumocytes, Intestine and Kidneys, tissue damage will evoke inflammatory response which may usher in respiratory distress, severe hypoxia and organ failure.
- Silent hypoxia may give a false sense of well-being in patients & may also deceive clinician.
- Routine use of pulse oximeter on admission & at frequent intervals is mandatory.
- We will have to fill gaps in understanding of the natural history of infection to fight the infectiousness and transmissibility.
- Better understanding of asymptomatic infection is required.
- We should promote point of care diagnostic tests.
- At least 1 hour time gap should be maintained between 2 cases to keep air exchange in operation theatre.
- Adequate protective measures should be used in all cases irrespective of the Covid status of the patients.
- Existing serological tests to be validated including those that have been developed by commercial companies and establishment of Bio banks and serum panels of well characterized Covid-19 sera to help such efforts.
- Work on animal models for vaccine and therapeutic research and development must be encouraged and promoted.
- SARS-COV-2 & COVID-19 though they are antigenetically similar they are not the same virus.

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