International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Timely Appropriate Dynamic Doses of Corticosteroid: Life Changer in COVID-19 Management as Home based Care of COVID Patient through Proper Monitoring by Teleconsultation

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Keywords: Microvascular coagulation, cytokine storm

1. Introduction

After 1st wave of COVID-19 second wave for COVID-19 pandemic, in India, has devastated hospitals (Government and Private) by having long queue of ambulances to enter the premises due to non availability of beds or ICU or oxygen supply specifically in big metro cities like Delhi and Mumbai, Ahmedabad etc. This has not been restricted to hospital line-ups but also run out for cremation space with a waiting list for people to be cremated with full honor. However, report from village, town and small cities is still to be anticipated [1].

The current situation with the pandemic of coronavirus (COVID-19) is no exception for precipitating fault lines that contributes to the disaster. [2]

In-order to decrease the hospital admission load for mild to moderate cases and severe case early to prevent mortality of serious sick patients due to delayed or non availability of hospital admission can be overcome by having telemedicine consultation and counseling of mild to moderate patient and severe also.

Deployment of telemedicine as a substitute for in-person care throughout the country and worldwide was aimed at achieving the triple objectives of (1) caring for the patients requiring isolation and intensive care, (2) continuing to care for customary patients, and (3) protecting providers and patients from infection. [2]

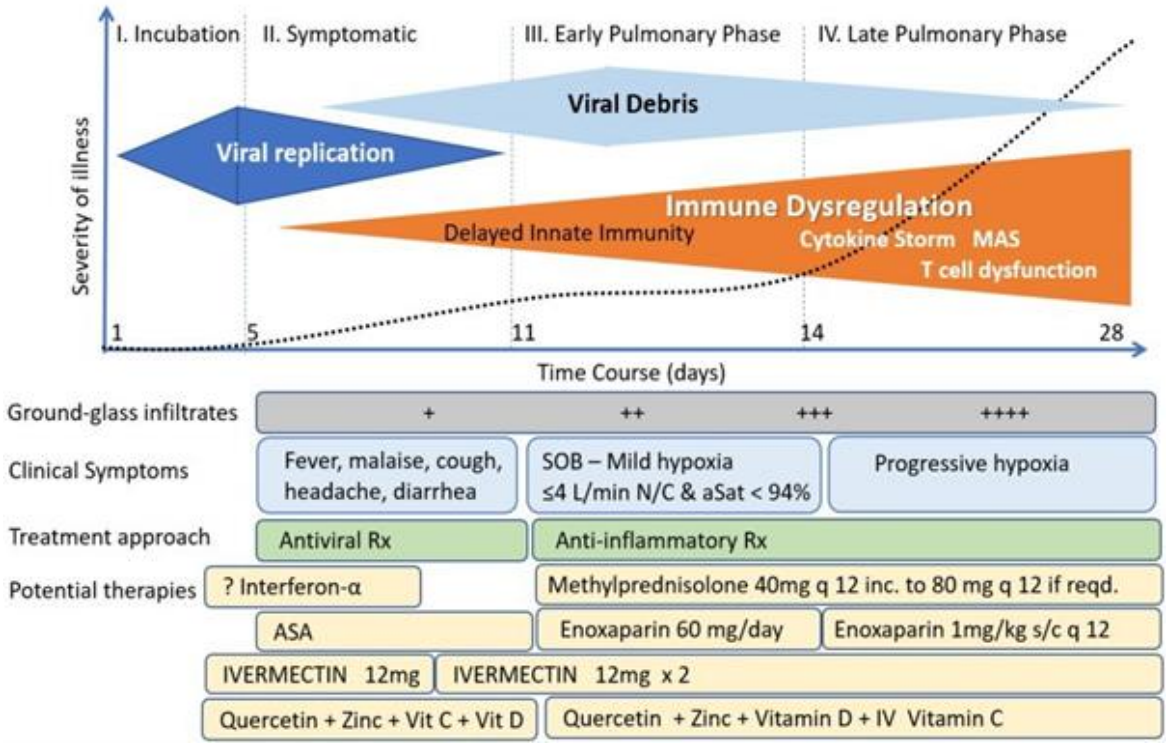

Figure 1: (Different phases of COVID-19 infection and Treatment)

Looking at the present upsurge of the second pandemic wave we, with our 18 years of clinical experience in respective specialty started giving telemedicine consultation and counseling to diagnosed COVID family members and friends were we not only prescribed them the appropriate medication as per the guidelines for OPD basis but also identified early hospitalization required for the respective patient depending on the Clinical criteria, biochemical and SpO2 trends, Pulse Rate and temperature monitoring at home by the by patient with proper monitoring charts that sample chart attached with this presentation also to help others with their clinical symptoms which they could explain telephonically. Monitoring the CBC, CRP Serum ferritin is of great help in treatment protocol to detect severity early,

Most important is proper monitoring of all positive or false negative symptomatic patient of family with proper monitoring sample charts and by clinical and biochemical and Spo2 trends because 80 to 85 of patients are mild not required specific treatment but rest 10 to 15 % may be moderate to severe and detection of these patients early and treatment with proper doses of medicine and proper tapering is primarily important. Minimal dose of steroids 80 mg prednisolone or methylprednisolone but we used Tab prednisolone for orally in our OPD patients and intravenous methyl prednisolone in admitted as glucocorticoid activity, one set of action and t1/2 (half life) of both is nearly same.

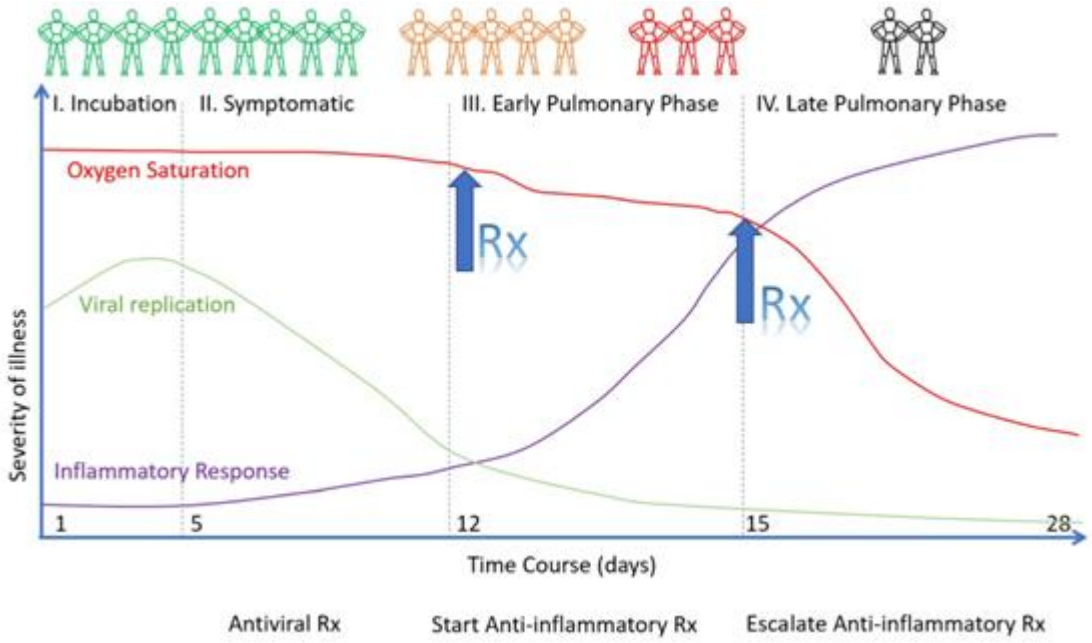

Figure 2: (Dynamic doses of Anti-inflammatory agent according to severity of hypoxia)

was given for minimum 7 day and subsequent tapering depends on clinical, biochemical and SpO_2 trends but may required escalation to 120 BD or more and if response is poor pulse doses of 250 to 500 mg required [4 –16]. Observational and randomized studies have clear demonstrated superiority of methyl prednisolone over low dose dexamethasone. [17, 18]

Most important is proper tapering of drug in next 2 to 3 wk to deal with ongoing inflammation and prevention of interstitial lung fibrosis and effect of corticosteroid on profile of dysregulated immune markers is clearly illustrated. [19]

Steroids should be avoided in symptomatic phase (less than 5 days of initiation of symptoms) since it can increase the viral replication and proportional Inflammation also and thus can lead to further damage in terms of inflammatory reaction [20]), it should be noted that when corticosteroid used after replication phase means even in early pulmonary phase do not increase viral shedding or decrease the production of type of specific antibodies for protection of re-infection [9, 73]. Only indication of early steroid is in high risk cases with presentation of hypoxia in early phase itself.

Our Practice and experience

According to our observation and the inputs from the research, the most important part in COVID management is proper monitoring and detection of moderate or severe patients and timely treatment with proper dosage.

Our aim is to prevent the hospital load by providing telemedicine management to COVID patients using a proper course of prednisoloneoral tablets to those detected moderate to severe patient by our monitoring.

Dosage of steroids is extremely dynamic; this cannot remain identical for every patient, like researchers have identified in WHO Study [21] in which same low dose is recommended. Some might require lower dose of 80 mg day, while few might require higher pulse therapy of 1 gm/day. [4- 16]

Our experience, with approximately 2500 patients, in which majority of patients detected mild in each family but 257 detected moderate according to our clinical, biochemical and spo2trends criteria and treated properly will proper does of steroids but some patients presented late as moderate to Severe hypoxia are admitted and treated like with high flow 02 or BIPAP due to massive cytokine storm and given bolus

of 1 gm pulse therapy of methyl prednisolone and then infusion of 1 gm in 24 hour and then decrease progressively.

Out of total 2500 patients and 257 moderate to Severe 2 death reported. One patient consult very late with severe hypoxia and second was a stable patient but had sudden cerebrovascular ischemic stroke even after Ecosprin150 and Rivoraxaban oral anticoagulant is going on.

Atorvastatin 80 mg per day in very high risk and 40 mg per day [22 26] in all moderate case till 4 to 6 weeks and ecosprin 150 [27, 28, 29, 30, 31] in very high risk and 75 in all moderate case for 8 weeks are important to prevent microvascular coagulation and Acute coronary events because of even minimal Inflammation in their coronaries.

Control of blood sugar is very important. Hb1AC value (5.7 to 6.5) indicates pre-diabetic state while value more than 6.5 should be diabetic. The estimation of Hb1AC is important to identify undiagnosed diabetic patients so that it will be easy for physician can monitor and control patients sugar level.

Clinical case strategies

Our instructions to patients was to prepare a chart showing values for SpO2, HR, temperature and other associate symptoms and message it at least thrice a day. Indication for increased inflammatory reaction was identifies by these criteria's:

- Persistent fever for more than 5days.
- Reappearance of fever after 5thday.
- Feeling of weakness, fatigue or malaise after 5 th day.
- Tachycardia (HR more than 100b/min) after 5 th day.
- Decrease SpO2 trends Ok (e. g., from 98 to 95).

Lab Investigation markers: 3 rd day, 6 th day 9 th day.

- Decreased trends of TLC, platelet count, Absolute lymphocytes or increased N/L ratio.
- Raising trends in CPR, S. ferritin, LDH.

Case-1

A 68 year old male with various co-morbities; Diabetic since past 20 years on insulin 52 unit per day and with oral hypoglycemics, hypertensive since past 28 years and on multiple antihypertensive drugs, suffering from pepticulcer, with fatty liver, dyslipidemia, and was chewing tobacco since past 40 years although a regular morning walker for 45 minutes.

The episode began with complain of throat pain with mild fever. RTPCR report showed positive on **4thday** by then patient had mild throat irritation and no fever. Patient was already on Ecosprin150 and atorvastatin10 from day 5 and Atorvastatin40 was added

5th day: Lab reports; Total Leucocyte count (TLC) 4200, Lymphocyte percentage (L) 63%, Platelet count (pc) 2.8, C-Reactive protein (CRP) 1.2, S. Ferritin7.4 with SpO2 value 97 to 99

8th Day: Lab reports; TLC 4000, L 34%, pc 3.1, CRP 1.4, S ferritin10.2, with SpO2 value 97 to 99 no fever, but mild throat irritation

12th day: Reappearance of fever 99 to 100^{0}C, SpO2 value dropped to 94 to 95.

Lab reports-TLC 4340, L 33%, pc 2.9, CRP 13.4, S ferritin38.

2 tablets of Omnacortil 40 stat followed by Omnacortil 60 mg for 5 days with proper monitoring of sugar levels at two intervals (fasting pre-lunch and pre-dinner) and modify by insulin and oral hypoglycemic drug doses. Fever stopped immediately after intake of first dose of Omnacortil with less throat irritation. SpO2 value rose to 95 to 96.

Markers were repeated on 15th day to decide 60 mg Omnacortil for 2 more days or taper subsequently.

15th day: Lab reports; TLC 5360, L 43%, PC 2.93, CRP 4.3, S ferritin 26, SpO_2 97 to 98, Omnacortil tapering was done starting from 40 mg for 5 days, then 30 mg for 5 days, 20 mg for 4 day, 10 mg for 4 day and finally 5 mg for 4 days then stoppage so as to deal ongoing inflammation.

Now patient is fit and fine continuing with drugs for DM and breathing exercise

Case-2

A 58 year old female patient, wt106 kg, patient was depressed with less physical mobility having hypothyroidism and diagnosed with Diabetes Mellitus during COVID state with Hb1AC value 6.9.

Day-1: First symptom of cough and cold

3rd day: SpO_2 was 86, and was admitted to a hospital LMH, Remdisivir, an antibiotic and Ecosprin was started.

5th Day: SpO_2 89 in-spite of 15L Oxygen. Physician had not started steroid since CT was normal and stated that the acute phase reactant are not favoring. Our experience in the field convinced the physician 80 mg methyl Prednisolone BD with and 4 cc Dexona; keeping in mind that we are supposed to treat the patient based on clinical sign and symptoms rather than investigation because investigation can confuse you but not hypoxia in COVID-19.

6th Day: At morning SpO_2 rose to 96 with 6Liters of Oxygen

Pt. was on remdisivir, ivermectin, Doxy, LMH from the day of hospital admission without steroids. However addition of steroid drastically improved the condition of the patient in ICU.

After 4 days of hospital treatment patient discharged with tapering doses for Prednisolone (80 mg for 4 days, then 60 mg for 4 days, then 40 mg for 4 days, followed by 20 mg for 4 days lastly 10 mg and 5 mg for subsequent 4 days). Atorvastatin 40 and Ecosprin 75 were continued for next 1 month along with and tab Rivoraxaban (oral anticoagulant) for next 2 wk. Patient was instructed to continue vitamins and breathing exercises.

Patient is perfectly doing good today.

Case-3

A 72 year old male undergone angioplasty, hypertensive since past 20years, overweight and was recently diagnosed for diabetes mellitus with Hb1AC 6. 6 although had been doing regular walking.

Patient presented viral like symptoms but with good general condition on 29 Nov.

He was advised to go for COVID test but refused. On our request, he went for blood investigations like CRP and TLC.

Day-2 morning: Lab reports; CRP 147, SpO2 varied from 96 to 98, refused hospital admission.

Day-2 evening: SpO2 dropped to 91, by the time patient was admitted to hospital SpO2 dropped to 79. However, patient was kept. On BIPAP, pressure support 20, PEEP 8 (PIP28), FiO2 100and SpO2 91

Hospital treatment was initiated with an antibiotics, Ecosprin150, Clexan0.4 cc bid, Atorvastatin40 mg bid and we convinced the in-charge physician to started inj methyl Prednisolone 1 gm stat in 100 ml Normal Saline. Followed by 1 gm iv Infusion for next 24 hour.

Day-3: SpO2 95 with P support 16 PEEP 6 (PIP 24) Fio2 60%CRP, 145, S ferritin more then 1500.

Day-4: P support 14PEEP 5 (PIP 19), Fio2 50% and SpO2 94

Day-5: Lab reports CRP 131, S ferritin more than 1500 but P support 12 PEEP 5 (PIP 17), Fio2 40%, SpO2 value ranged 94 to 95.

Methyl Prednisolone Infusion was decrease to 500 mg per 24 hour and subsequently progressively reduced.

Day-6: Lab report CRP 72 and S ferritin decreased to 720. This showed that massive cytokine storm could be curbed by timely addition of steroids i. e., adding more water till whole of the fire stops, thus no further propagation of even a spark of fire this implies that the timely doses of steroid depending on severity of hypoxia and Inflammation is the most important part in treatment of this reaction.

Day-7: Patient seemed depressed and developed psychotic signs, so Placcida 0.5 bd was initiated. Within 12 hours of medications patient was stable. During that time Troponin1 was done which was within normal range

Day-8: Patient was discharged on patient's persistent request. Troponin1 and Procalcitonin were done before discharges which too were normal. At the time of discharge SpO2 value was 93 on 4 Lit Oxygen which was arranged at home. Lab report; CRP 5.8, S ferritin 570, D Dimer4500.

In-spite of high d dimer value patient was given DAMA. D-dimer reflects the production of cross-linked fibrin and can be a misleading marker, since its value is raised in patients having hepatic or heart disease.9

Discharge Treatment: Oral tab Prednisolone160 mg 4 days, 120 or next 4 days, 80 for 4 days, 60 for 4 days, 40 for 4 days, subsequently 20, and 10 for 4days, then 5 and lastly 2.5 for 3 weeks.

Tapering of steroid for last 5 mg and 2.5 mg should be slow so as to prevent lung fibrosis especially in such type of who were on BIPAP or High flow 02.

Tab Rivoraxaban 10 mg for 3weeks. Ecosprin and Atorvastatin 40 for lifelong due to post angioplasty.

Advised pranayam and breathing exercises with respirator for at least next 6 month. Regular breathing exercises like pranayam increases vital capacity.

Rich protein diet (24gms/day) with potassium supplement with music as well as message therapy has good home based outcome.

Day-16: SpO2 value 94 without supplement Oxygen

Patient is fit and fine even after 4 months of the disease.

This is steroid responsive disease and doses are extremely dynamic depends on severity of disease.

Case 4

A 35 year old male, known case of sickle cell disease diagnosed with positive for COVID-19 with SpO2 value 87 He was on Hydroxyurea 1.5 gm daily, folic acid and other medicine

Day-1 presented to OPD: Lab reports- CRP 5.4, S ferritin more than 2000, Hb 7.7, TLC 3400, pc 1.85

Relatives were hesitant for hospital admission but were convinced looking at the parameters and clinical signs of the patient. They could arrange a trained nurse and O2 support at home. Thus injection Methyl Prednisolone 1 gm in 100 ml NS in over 1 hour was started followed by 250 mg iv 8 hourly for next 3 days

Day-2 post OPD: SpO2 value 91 without O2 support, however we started 2 lit Oxygen so as to maintain SpO2 of 95.

Inj (Low molecular heparin) 0. 6 cc sc was started with inj basal insulin of 15 units, so as take care of sugar level. The sliding scale of insulin requirements would be less because bolus doses of steroids to patient was given thus expected raised sugar level would be the result and if required use insulin according to sliding scale.

The Fluconazole 200 mg OD and 1 broad spectrum antibiotic was give, to prevent secondary bacterial and fungal infection. Ecosprin 75 1 OD and Atorvastatin 20 OD along with and Multivitamin, Zink 50 mg 1 OD, Vit D sachet weakly,

Day-3 post OPD: Lab reports- CRP 5, S. ferritin more then 2000, TLC 4500, pc 2.3, Hb 7. 6.

Patient still was on 2 lit Oxygen with methyl Prednisolone 250 Tds.

Being a sickle cell patient he started developing severe pain Cross striated, thus high doses of Tramadol 100 mg 1 tab every 6 hourly Brufen 400 mg every 6 hourly started simultaneously.

Day-6 post OPD: He was quite comfortable with intermittent episodes of severe pain.

Spo2 94 without O2 support.

Lab reports -- Hb 7.4, TLC 34000, pc 2.8, S ferritin 1650, CRP 4.2, Procalcitonin normal

Thus, we decided to taper the steroid doses; Methyl Prednisolone150 mg TdS for next 2 days. Rest treatment same continue

Day-8 post OPD: Patient did not require any oxygen support although had intermittent pain episode but comfortable.

Lab report-- Hb 7.7, TLC 54000, pc 2.7, CRP 5.3, S ferritin 789

In spite high counts Procalcitonin still was normal, as expected that inflammatory steroid causes high WBC, it is not because of secondary bacterial Infection.

Methyl Prednisolone120 mg tds for 3 day, then 80 Tds for 3 days finally start on oral tablets of Prednisolone 40 mg (4 Tab for 4 days, 3 for 4 days, 2 for 4 days then 1 for 4 Days)

Day-10 post OPD: Lab report-- Hb 7.3, TLC 22000, CRP 4.4, S ferritin 138

Now the patient is doing good with intermittent pain

2. Discussion

COVID-19 is a viral infection, as it is mild in 80 to 85 % of patients but rest 10 to 15 % may have moderate to severe disease, if we see basic pathogenesis of these moderate to severe patients it is Infection associated disproportionate Inflammation, we can give different name like cytokine storm or Macrophage activation syndrome or infection associated HLH (hemophagocytic lymphohistiocytosis) [32–44] so host immune disproportionate response to virus rather than virus itself which is killing the host [45 46, 47, 4839-441], damage our vital organ like lungs is most commonly affected organ. Patients presented as hypoxia but it is systemic inflammatory disease it can damage heart and other organ also and because of inflammatory damage of our vascular endothelium [45, 49, 50, 51] causing release of large aggregate of vvf and ACE 2 receptor on platelets causes massive platelet Aggregation [52, 31, 53] and then microvascular coagulation and it impair blood flow [54-67], creates VQ mismatch (ventilation perfusion mismatch) and it should be noted that the thrombotic microangiopathy appear to target predominantly pulmonary and cerebral circulation [38]. It is important other mechanism of hypoxia with parenchymal inflammatory lung damage [38, 52] and many patient may have cerebrovascular ischemic stroke also so there is role of Anti-inflammatory agent Corticosteroid, Anti platelet drug like Aspirin [28, 29, 30, 31], Anticoagulation like low molecular heparin (clexan) [66-72] to manage both inflammatory parenchymal da mge and microvascular coagulation. Most important is doses of steroids because disease is so dynamic 85 % required nothing only vitamins and paracetamol few required 1 gm bolus of methyl Prednisolone. If patient is presented in early pulmonary phase with mild hypoxia 80 mg is sufficient but if presented in late pulmonary phase with moderate to severe hypoxia like and on high flow 02 or on BIPAP may require 500 to 1 gm bolus and then 150 mg to 250 mg tds for next 3 days. it is because grades of Inflammation and proportional damage of organ is severe in these patients that is reflected in biochemical markers like CRP and ferritin also. Dynamic doses of steroids depend on severity of hypoxia and early aggressive Anti-inflammatory therapy is primarily important to improve oxygenation and decreases requirement of O2 to patient. It drastically decrease patients stay in ICU and 02 dependency and chances of secondary bacterial infection or fungal infection also decreases because of prolonged stay in ICU.

3. Conclusion

By proper Monitoring of COVID patients per family, we can detect those 10 to 15 %moderate to severe patient early by our clinical, biochemical and Spo2 Trends and can treat at home without doing CT chest in majority we can prevent lung damage with dynamic doses of steroids and if patient is presented late as moderate to severe hypoxia may required pulse doses of methyl-prednisolone.

In flames (Fire)
No fire – No water (steroid)
Minimal fire –Minimum water (80 mg) Methyl Prednisolone
Maximum fire – Maximum water (1 gm) Methyl Prednisolone

Sample Monitoring Chart 1

27	20-Apr	8:00 AM	97	64	97		109	98	82	97.9		201
28		2:00 PM	96	80	98.2			98	80	98.3		
29		8:00 PM	97	72	97.6		343	98	81	97.7		389
30	21-Apr	2:00 AM	97	87	97.1		68	98	90	98		99
31		8:00 AM	95	88	97.8			98	90	99.6		
32		2:00 PM	97	79	98		362	97	80	97.7		538
33	22-Apr	8:00 PM	97	77	96.9		78	98	77	97.1		133
34		2:00 AM	97	89	96.8			98	76	98.6		
35		8:00 AM	97	90	97.4		415	98	80	97.7		446
36	23-Apr	2:00 PM	97	65	97.8		110	98	70	97.6		144
37		8:00 PM	96	86	96.7			98	95	99.2		
38		2:00 AM	96	77	97.3		318	98	90	98		388
39	24-Apr	8:00 AM	96	77	97.4		130	98	79	97.7		141
40		2:00 PM	96	85	97.1			98	78	97.9		
41		8:00 PM	96	86	98.3		396	98	80	97.9		375
42	25-Apr	2:00 AM	98	75	97.7		103	98	80	97.8		205
43		8:00 AM	96	88		105/68		98	79	97.7	106/65	
44		2:00 PM	96	74	97.2		307	98	80	97.5		377
45	26-Apr	8:00 PM	96	74	97.4		112	98	79	97.7		240
46		2:00 AM	96	85	97.8	110/70		98	80	97.1	114/72	
47		8:00 AM	96	84	97		323	98	74	97.5		424
48	27-Apr	2:00 PM	97	82	97.1		99	98	75	97		251
49		8:00 PM	97	85	97.7			98	74	97.5		
50		2:00 AM	96	84			256	98	81	97.3		418
51		8:00 AM										

		28th April Morning (Initial date)			28th April Evening (Initial date)			Not well from 22nd April from the day of second vaccination			Deepa Sugar
		Oxygen	Pulse	Temp	Oxygen	Pulse	Temp	Oxygen	Pulse	Temp	
29-Apr	01:00 AM	97	120	100.5	97	129	99.5	98	92	98	
30-Apr	09:30 AM	98	109	98.9	97	125	98.9	97	91	99.4	
	03:30 PM	97	105	99.4	96/97	120	97	98	97	99.1	
	09:30 PM	97	97	99.7	97	127	101.4	98	86	98.9	
01-May	09:30 AM	98	90	98.6	98	100	100.6	98	87	98.9	
	04:00 PM	98	89	98.9	98	105	98.6	97	114	99.6	
	09:30 PM	98	98	99.4	98	101	98.9	98	82	99	
02-May	09:30 AM	98	90	98.6	98	91	97.9	97	93	99	
	03:50 PM	98	98	98.6	98	102	98.7	97	103	99.3	
	09:30 PM	98	88	98.5	98	114	97.8	98	75	98.3	
03-May	09:30 AM	98	84	98.6	98	100	97.9	97	85	99	
	03:30 PM	98	92	98.8	98	95	97.9	97	83	98.9	
	09:30 PM	98	90	98.9	98	104	98.6	97	85	98.3	
04-May	09:30 AM	98	91	98.7	98	105	97.1	97	82	98.6	
	03:30 PM	98	91	99.1	98	105	97.9	97	87	98.7	
	09:30 PM	97	110	98.6	98	115	97.9	97	82	98.6	
05-May	09:30 AM	98	102	97.4	98	105	97.4	97	82	98.1	
	03:30 PM	97	105	96.9	98	99	97.6	97	93	98.7	
	09:30 PM	97	104	98.6	98	95	97.6	97	75	98.7	
06-May	09:30 AM	97	89	97.6	98	100	97.1	97	80	98.3	
	03:30 PM	97	80	98.1	99	84	97.4	97	82	98.6	
	09:30 PM	97	99	97.9	97	99	97.3	97	83	98.1	
07-May	09:30 AM	97	98	97.9	98	108	97.4	97	80	98.3	
	03:30 PM	97	78	98.1	98	90	97.4	97	90	98.3	
	09:30 PM	97	82	97.9	98	93	98.1	97	77	98.1	
08-May	09:30 AM	97	77	98	98	94	97.2	97	81	98.1	
	03:30 PM	98	81	97.6	98	90	98.6	98	88	99.2	
	09:30 PM	98	73	98.6	98	92	98.6	97	85	98.6	
09-May	09:30 AM	98	76	97.6	98	96	96.9	97	78	98.1	
	03:30 PM	98	87	97.9	97	100	97.7	97	91	98.9	
	09:30 PM	98	93	97.9	98	90	97.6	98	79	98.6	
10-May	09:30 AM	97	80	97.9	98	100	97	98	80	98.4	95 (Fasting)
	03:30 PM	98	79	97.6	98	99	98.3	98	94	98.6	
	09:30 PM	97	80	98.1	98	100	97.9	97	90	98	

References

[1] https: //www.bbc.com/nfews/world-asia-india-56913047

[2] Rashid L. Bashshur, Charles R. Doarn, Julio M. Frenk, Joseph C. Kvedar, Gary W. Shannon, and James O. Woolliscroft. Telemedicine and e-Health. Nov 2020.1310-1313.

[3] In this U-tube video, Professor Britt Glaunsinger, PhD provides an outstanding review on the molecular virology of SARS-CoV-2: https: //www.youtube.com/watch?v=DQVpHyvz4no

[4] by Paul Marik, MD reviewing clinical aspects of COVID-19. https: //www.youtube.com/channel/UCz9Pvn15m4Rv1uY-aBYRVuw4.

[5] Villar J, Confalonieri M, Pastores SM, Meduri GU. Rationale GU Prolonged corticosteroid treatment in the acute respiratory distress syndrome caused COVID-19. Crit Care Expl 2020; 2: e0111.
[6] Fadel R, Morrison AR, Vahia A et al. Early course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 2020; 71: 2114-20.
[7] Chroboczek T, Lacoste M, Wackenheim C, Challan-Belval T, Amar B, Boisson T. Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. medRxiv 2020.
[8] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020.
[9] Cruz AF, Ruiz-Antoran B, Gomez AM, Lopez AS. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: A retrospective controlled cohort study. medRxiv 2020.
[10] Liu J, Zheng X, Huang Y, Shan H, Huang J. Successful use of methylprednisolone for treating severe COVID-19. J Allergy ClinImmunol 2020.
[11] Meduri GU, Bridges L, Shih MC, Marik PE, Siemienluk RA, Kocak M. Prolonged glucocorticoid treatment is with improved ARDS outomces: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med 2016; 42: 829-40.
[12] Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19. A meta-analysis. JAMA 2020.
[13] Ruiz-Irastorza G, Pijoan JI, Bereciatua E, Dunder S, Dominguez J, Garcia-Escudero P. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. medRxiv 2020.
[14] Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC. Effect of dexamethasone on days alive and ventilaor-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19. The CoDEX randomized clinical trial. JAMA 2020.
[15] Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S. Intravenous methylprednisolone pulse as a treatment for hospitalized severe COVID-19 patients: results from a randomised controlled clinical trial. EurRespir J 2020.
[16] Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19. The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA 2020.
[17] Dequin PF, Heming N, Meziani F, Plantefeve G, Voiriot G. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19. A randomized Clinical trial. JAMA 2020.
[18] Ranjbar K, Shahriarad R, erfani A, Khodamoradi Z, Saadi MH. Methylprednisolone or dexamethasone, which one is the superior corticosteroid in the treatment of hospitalized COVID-19 patients: A triple-randomized controlled trial. Research Square 2021.
[19] Ko JJ, Wu C, Mehta N, Wald-Dickler N, Yang W. A comparison of methylprednisolone and dexamethasone in intensive care patients with COVID-19. medRxiv 2021.
[20] Wang SY, Chang CH, Meizlish ML, Bahel P, Rinder HM. Changes in inflammatory and immune drivers inresponse to immunmodulatory therapies in COVID-19. medRxiv 2020 20. Effect of Dexamethasone in hospitalized patients with COVID-19-Preliminary report. N Engl J Med 2020.20. Kow CS, Hasan SS..
[21] Effect of Dexamethasone in hospitalized patients with COVID-19-Preliminary report. N Engl J Med 2020.21. Zhang XJ, Qin JJ, Cheng X et al. a
[22] Who Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O, Cavalcanti AB, Dequin P-F, Du B, Emberson J, Fisher D, Giraudeau B, Gordon AC, Granholm A, Green C, Haynes R, Heming N, Higgins JPT., Horby P, Jüni P, Landray MJ, Le Gouge A, Leclerc M, Lim WS, Machado FR, McArthur C, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020; 324: 1330–1341.
[23] In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. Cell Metabolism 2020.
[24] Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, Chung CW. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. Crit Care 2020; 24: 429.
[25] Gupt. a A, Madhavan MV, Poterucha TJ, DeFilippis EM, Hennessey JA. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. Research Square 2020.
[26] Kow CS, Hasan SS. Meta-analysis of effectiveness of statins in patients with severe COVID-19. Am J Cardiol 2020.
[27] Tan WY, Young BE, Lye DC, Chew DE, Dalan r. Statin use is assocaited with lower disease severity in COVID-19 infection. Nature Research 2020.21. Tan WY, Young BE, Lye DC, Chew DE, Dalan r. Statin use is assocaited with lower disease severity in.
[28] Varatharajah N. COVID-19 CLOT: What is it? Why in the lungs? Extracellular histone, "auto-activation" ofprothrombin, emperipolesis, megakaryocytes, "self-association" of Von Willebrand factor and beyond. Preprints 2020.
[29] Cloutier N, Allaeys I, Marcoux G, Machius KR, Mailhot B. Platelets release pathogenic serotonin and return to circulation after immune complex-mediated sequestration. PNAS 2018;E1550-E1559.
[30] Hottz ED, Azevedo-Quintanilha Ig, Palhinha L, Teixeira L, Barreto EA. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in. patients with severe COVID-19. Blood COVID-19 infection 2020; 136: 1330-1341.
[31] Barrett TJ, Lee AH, Xia Y, Lin LH, Black M, Cotzia P. Platelet and vascular biomarkers associate with

thrombosis and death in coronavirus disease. Circulation Research 2020; 127: 945-7.
[32] Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. Journal of hematology & oncology 2020; 13: 120.
[33] Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Febratinib. J MicrobiolImmunol Infect 2020.
[34] Bryce C, Grimes Z, Pujadas E et al. Pathopysiology of SARS-CoV-2: targeting of endothelial cells renders a complex disease with thrombotic microangiopatthicandaberrant immune response. The Mount Sinai COVID-19 autopsy experience. medRxiv 2020.
[35] McGonagle D, Sharif K. The role of cytokines including interleukin-6 in COVID-19 induces pneumonia and macrophage activation syndrome-like disease. Autoimmunity Reviews 2020.
[36] Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
[37] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z. Clinical course and risk factor for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020.
[38] Giamarellos-Bourboulis EJ, Netea mg, Rovina N, Akinosoglou K.complex immune dysregulation in COVID-19 patients with severe respiratory failure. medRxiv 2020.
[39] Qin C, Zhou L, Hu Z, Zhang S. Dysregulation of the immune response in patiens with COID-19 in Wuhan, China. Lancet Infect Dis 2020.
[40] Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 recept. or (IL-6R) antagonsitTocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 2020.
[41] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the "Cytokine Storm" in COVID-19. J Infection 2020.
[42] Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020.
[43] Tay MZ, Poh CM, Renia L, MacAry PA. The trinity of COVID-19: immunity, inflammation and intervention. Nature Reviews 2020; 20: 363-74.
[44] Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P. Pulmonary post-mortem findings in a series of COVID-19 ccases from northern Italy: a two-centredescript. ive study. Lancet Infect Dis 2020; 20: 1135-40.
[45] Hariri LP, North CM, Shih AR, Israel RA. Lung histopathology in COVID-19 as compared to SARS and H1N1 influenza: A systematic review. Chest 2020.
[46] Dorward DA, Russell CD, Um IH, Elshani M, Armstrong SD, Millar T. Tissue-specific immunopathology in fatal COVID-19. Am J RespirCrit Care Med 2020
[47] Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med 2020; 46: 1105-8.
[48] Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nature Reviews 2020.
[49] Varga Z, Flammer AJ, Steiger P, Habrecker M, Andermatt R, Zinkernagel AS. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020.
[50] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T. Pulmonary vascular endothelialitis, Thrombosis, and Angiogenesis in COVID-19. N Engl J Med 2020; 383: 120-8.
[51] Barrett Tj, LeeAH, XiaY, LinLH, BlackM, Cotzia P,. Platelet and vascular bomarker Associated with thrombosis and death in coronavirus disease. Circulationreasearch 2020; 127: 945-7.
[52] Kory P, Kanne JP. SARS-CoV-2 organizing pneumonia: "Has there been a widespread failure to identify and treat this prevalent condition in COVID-19?'. BMJ Open Resp Res 2020; 7: e000724.
[53] Torrealba JR, Fisher S, Kanne JP, Butt YM, Glazer C, Kershaw C. Pathology-radiology correlation ofcommon and uncommon computed tomographic patterns of organizing pneumonia. Human Pathology 2018; 71: 30-40.
[54] Bikdeli B, Madhavan MV, Jimenez, Chuich T, Dreyfus I. COVID-19 and thrombotic or thromboembolic : Implications for prevention, antithrombotic therapy, and follow-up. J Am CollCardiol 2020
[55] Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020.
[56] Klok FA, Kruip MJ, van der Meer NJ, Arbous MS. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis Research 2020.
[57] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 with coagulopathy. medRxiv 2020.
[58] Zhai Z, Li C, Chen Y, Gerotziafas G, Zhang Z. Prevention and treatment of venous thromboembolism assocaited with Coronavirus Disease 2019 Infection: A consensus statement before guidelines. ThrombHaemost 2020..
[59] Paranjpe I, Fuster V, Lala A, Russak A, Glicksberg BS. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patietns with COVID-19. J Am CollCardiol 2020.
[60] Iba T, Levy JH, Levi M, Connors JM. Coagulopathy of coronavirus disease 2019. Crit Care Med 2020.
[61] Joly BS, Siguret V, Veyradier A. Understanding pathophysiology of hemostasis disorders in critically illpatients with COVID-19. Intensive Care Med 2020; 46: 1603-6.
[62] Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020; 46: 1089-98.
[63] Varatharajah N, Rajah S. Microthrombotic complications of COVID-19 are likely due to embolism of circulating endothelial derived ultralarge Von Willebrand Factor (eULVWF) decorated-platelet strings. Federal Practitioner 2020.

[64] VWF. Du L, Kao RY, Zhou Y, He Y. Cleavage of spike protein of SARS coronavirus by protease factor Xa is associated with viral infectivity. Biochemical & Biophysical Research Communications 2007; 359: 174-9.
[65] Sardu C, Gambardella J, Morelli MB, Wang X. Is COVID-19 an endothelial disease? Clinical and basic evidence. m234. Ranjbar K, Shahriarad R, erfani A, Khodamoradi Z, Saadi MH. Methylprednisolone or dexamethasone, which one is the superior corticosteroid in the treatment of hospitalized COVID-19 patients: A triple-blinded randomized controlled trial. Research Square 2021.
[66] Taccone FS, Gevenois PA, Peluso L, Pletchette Z, Lheureux O. Higher intensity thromboprophylaxis regimens and pulmonary embolism in critically ill coronavirus disease 2019 patients. Crit Care Med 2020.
[67] Buijsers B, Yanginlar C, Maciej-Hulme ML, de Mast Q. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. EBioMedicine 2020.
[68] Kim SY, Jin W, Sood A, Montgomery DW, Grant OC, Fuster MM. Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions. Antiviral Res 2020; 181: 104873.
[69] Clausen TM, Sandoval DR, Spliid CB et al. SARS-CoV-2 infection depends on cellular heparansulphate andACE2. bioRxiv 2020.
[70] Kwon PS, Oh H, Kwon SJ et al. Sulphated polysaccharides effectively inhibit SARS-CoV-2 in vitro. Cell Discovery 2020; 6: 50.
[71] Huang X, Han S, Liu x, Wang T, Xu H. Both UFH and NAH alleviate shedding of endothelial glycocalyx and coagulopathy in LPS-induced sepsis. Exp Thera Med 2020; 19: 913-22.
[72] Buijsers B, Yanginlar C, de Nooijer A, Grondman I, Jonkman I, Rother N. Increased plasma heparanase activity in COVID-19 patients. medRxiv 2020.
[73] Dayer MR. Coronavirus (2019-nCoV) deactivation via spike glycoprotein shielding by old drugs, bioinformatic study. Preprints 2020.
[74] Salton F, Confalonieri P, Santus P et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. medRxiv 2020.