Academy of Advanced Medical Education

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Presents

TREATMENT OPTIONS FOR COVID-19

SYNOPSIS

15th August 2020

7pm to 8.30 pm

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MODERATOR

Panel Members

Prof. Dr. Randeep Guleria

(Padma Shri & Dr. B.C. Roy Award)

MBBS, MD, DM

Director, All India Institute of
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Dr. Deepak Talwar

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Senior Consultant & Chairman-
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Dr. Agam Vora

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Senior Pulmonologist &
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Dr. Raja Dhar

MBBS, MD, CCT, FCCP, MSc

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Dr. Bamin Tada

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Secretary, TB association of NE India,
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Subject H is a 32 year old male with the following clinical features: 32 /M (Subject H)

- H/O low grade fever for 3 days along with bodyache, headache & myalgia.
- No Co-morbidities
- P-100/min
- T- 99.5F
- SpO2 – 98%

Investigations

- TC:5400 DC:N66, L30, E3, M1
- Platelets: 1.75 L
- SGPT: 42
- CRP: 3.5 mg/L
- COVID-19 RT PCR: + ve
- XRC – Normal
- Opted for home quarantine

P: Pulse T: Temperature SpO2: Oxygen Saturation TC: Total Count DC: Differential Count N: Neutrophils L:Lymphocytes E: Eosinophils M: Monocytes SGPT: Serum Glutamic-Pyruvic Transaminase CRP: C- Reactive Protein RTPCR: Reverse Transcription Polymerase Chain Reaction

Subject F is a 62 year old male with the following clinical features: 62 /M (Subject F)

- H/O low grade fever for 2 days along with bodyache
- H/O difficulty in breathing since 1 day
- H/O PTCA done 2 years back
- P-110/min
- T- 100.5F
- SpO2 – 85%

Investigations

- TC:4400, DC: P76, L20, E3, M1
- Platelets: 1.25 L
- SGPT: 52
- CRP: 45 mg/L
- COVID-19 RT PCR: +ve
- HRCT CHEST – CORAD VI

- Admitted to hospital and within a day shifted to ICU

PTCA: Percutaneous Transluminal Coronary Angioplasty HRCT: High-Resolution Computed Tomography

Subject M is a 60 year old female with the following clinical features: 60/F (Subject M)

- H/O low grade fever for 2 days along with bodyache
- H/O DM since 8 years
- P-100/min
- T- 100F
- SpO2 – 92%
- HGT- 375 mg/dl
- COVID-19 RT PCR: +ve
- Admitted to hospital

Subject W is a 29 year old female with the following clinical features: 29/ F (Subject W)

- Asymptomatic
- COVID-19 RT PCR: +ve
- Labs – WNL

DM: Diabetes Mellitus HGT: Hemo Glucose Test WNL: Within Normal Limits

Case Summary

- **Subject F – Father – ICU admission**
- **Subject M – Mother – Ward admission**
- **Subject H – Husband – Home quarantine**
- **Subject W – Wife – Asymptomatic COVID-19 +ve**

Q. What therapy will you offer to Subject W?
What is the role of 1)Vitamin C 2)Vitamin D 3)Zinc? Dosage?

- **Dr. Ketan Mehta :**

  We routinely recommend SMS
  S - Social distancing
  M – Mask
  S – Sanitizer

Even asymptomatic individual can safely receive vitamin C, vitamin D and zinc. There is no need to check the serum levels before starting the supplements. More than

90% of Indian population is vitamin D deficient, so it can safely be given unless someone is on a very high dose.

Dr. Agam Vora:

It is advisable to take all the supplements – Vitamin C, vitamin D and Zinc. They have some role in improving the immunity. They do no harm.

Dr. Randeep Guleria:

Vitamin C is usually given in the dose of 500 mg twice a day. There are no clear cut guidelines for zinc. Therefore, a multivitamin which has some degree of zinc preparation can also be given. Data regarding the role of these nutrients in immunity is not that strong. They do no harm and may provide some benefit, therefore can be given in mild or asymptomatic individuals.

Q. Where will you use Hydroxychloroquine (HCQ)?

Dr. Randeep Guleria:

Data currently is against the use of HCQs, however Indian guidelines still recommend it. In **mild cases,** HCQ can be used. **In healthcare workers coming in close contact with COVID-19 patients**, it can be used. Indian Council of Medical Research (ICMR) study showed a dose response relationship. Individuals who took loading dose followed by weekly dose have a tendency to have less COVID-19 infection. Data for mild cases is only from initial studies. Subsequent trials have not shown hydroxychloroquine to be very useful. It is a debatable issue. Therefore, if it has to be used, it can used in mild illness. **The dose is 400 mg twice a day with meals on day 1 followed by 400 mg once a day (dose can be split) with meals for the next 4 days.**Guidelines recommend that **close contacts of COVID-19 positive patients** should also be given HCQ. In higher risk group, Electro Cardio Gram (ECG) can be done.

Dr. Ketan Mehta:

HCQ itself does not cause QT prolongation if given alone, without any other drugs causing QT prolongation. ECG is not required when taken as a prophylaxis.

Q. Azithromycin/doxycycline – Preference?
For Husband/Mother/Father?
When will you prefer parenteral antibacterial? Which one?

Dr. Deepak Talwar:

Right now, we are using HCQ and azithromycin. If there is contraindication, then one can opt for combination of doxycycline plus ivermectin. **It will be given to home quarantined husband**. In **hospital set up, parenteral antibiotics** are given, either azithromycin or amoxycillin-clavulanic acid. In **ICU set up, broad spectrum antibiotics** should be given.

Q. Role of ivermectin? Dose & duration?
For whom? Subject Husband/Mother/Father H/M/F?

Dr. Raja Dhar:

Ivermectin is cheap, widely available and has lot of experience of use as an anti-parasitic. It causes significant reduction in virus in 48 hours in a cell culture. Data from clinical trials is still not available. Two trials, one form Bangladesh and one form Chile, have not given very robust evidence as far as clinical cure rates are concerned. However, there is reduction of

viral replication. In mild cases, ivermectin can be used. **The dosage regimen is 12 mg for 3 successive days.**

In very mild or mild patients, favipiravir will be the first line drug and if favipiravir is contraindicated, ivermectin will be the next choice. Ivermectin will be used for husband, not for mother and father.

It is better to start early. If used late the chance of mild disease going into severe disease is greater.

Q. Indications of steroids? For whom will you use? Subject Husband/Mother/Father? Choice of steroids? Dosage & duration?

Dr. Agam Vora:

If steroids are used too early and in very high dose, probably it may enhance the viral replication and there may be more of viremia. Steroids may not have role in early part of disease. When there is organizing pneumonia pattern, fibrosis, lung destruction or cytokine storm, one can use steroids. Literature goes more in favour of dexamethasone. However, the general trend is to use injection methylprednisolone 40 mg to begin with if there is moderate radiological involvement and if there is hypoxia. If there is not much of pulmonary

involvement and if patient is non hospitalized, there is no need of steroids. Steroids can be continued all throughout the cytokine storm and if patient is responding, it can be continued for 10 days to 2 weeks. Mother and father, both can be given steroids.

- **Dr. Raja Dhar:**

If patient needs oxygen to maintain saturations above 90%, steroids will be needed. The steroid of choice would be methylprednisolone, 40 mg twice a day. I will not use steroids in patients who do not need oxygen. Therefore, father would require steroids.

- **Dr. Randeep Guleria:**

Steroids are given in patients with **falling saturation, worsening of chest X ray** and patients with **moderate disease advancing towards severe disease.** We would use **methylprednisolone 0.5 – 1 mg/kg for duration of 5 days or 10 days.** 20 – 30% of asymptomatic positive individual may show patches on CT scan which will resolve on their own. Don't go by lung involvement in CT scan to decide on treatment for steroids. Look at the saturation and how patient is behaving. Steroids if started too early may lead to more viral replication and more deterioration of the patient. **If oxygen saturation falls below 93%, start considering steroids.**

- **Dr. Ketan Mehta:**

Steroids not required in mild to moderate cases not requiring oxygen.

Q. What is your experience with anti-viral combinations such as
Lopinavir + Ritonavir
Sofosbuvir + Daclastavir

- **Dr. Deepak Talwar:**

Sofosbuvir + Daclastavir combination is not used by me, therefore no experience. Lopinavir + Ritonavir was used prior to availability of remdesivir or favipiravir. **Now the antiviral spectrum is favipiravir and remdesivir .**

- **Dr. Ketan Mehta:**

In patients with both hepatitis C and COVID-19, Sofosbuvir + Daclastavir is a good option. But experience is limited.

Q. Favipiravir – For whom?
Subject – Husband/Mother/Father (H/ M/ F)? Duration?
Common Side Effects?

Dr. Agam Vora:

- **Favipiravir is used for mild to moderate cases.** It can be considered Subject H (Husband) and M (Mother). Subject H can be offered ivermectin + doxycycline or HCQ + azithromycin or favipiravir. The duration mentioned in literature is 14 days.
- If a ward patient deteriorates on favipiravir, it can be stopped, remdesivir can be started and shifted to ICU, if necessary. If the patient improves and becomes asymptomatic, favipiravir can be stopped on 5th or 7th day. If patient is in hospital and has radiological involvement it can be continued for full 14 days. There is no need to give the drug beyond 14 days.
- **Favipravir is extremely safe.** Loading dose of 1800 mg on day 1 can lead to loose motions. A lot of patients develop loose motions on day 2 or day 3 and it is a self-limiting loose motions. However, it is not understood whether the loose motions are due to drug or part of the disease process. If loose motions occur, is it sufficient to correct the fluid and electrolyte balance. There is no need for treatment with antimotility agents or any other drugs.

- Transient rise in SGPT AND SGOT, 2 – 3 times above the normal, is also noted. This can also because of extensive tests conducted in indoor patients. Otherwise there is no indication for the tests. This drug can give rise to elevation of uric acid levels. None of the patients complained of specific joint pain, they had joint pain which is always thought to be due to viral disease which settles on its own.

Dr. Randeep Guleria:

- **The data on favipiravir is more as compared to HCQ/ ivermectin.**
- Favipiravir was an anti-influenza drug introduced in 2014 for H1N1 and subsequently has been shown to have a wide antiviral activity. A randomized controlled trial where it was used for Ebola has shown positive results.
- The data for COVID-19 is not that strong. The one that is frequently quoted is published in a non-medical journal called Engineering. Therefore, there is a lot of debate over positioning of drug based on the evidence. Although the evidence for all the treatment options is not strong (ivermectin + doxycycline, HCQ + azithromycin or favipiravir), it is an individual choice how comfortable one is with using these drugs. We don't have enough evidence to say that one is better than other as of now. More head to head comparisons are needed.

Dr. Deepak Talwar:

Stopping of favipiravir at day 5 or day 7 should not be done rather can be given for 10 days. There is no data for 10 days, data is for 14 days only. Data is much stronger for remdesivir especially in case of Subject M who is admitted with 92% saturation. Subject M (Mother) is a candidate for early remdesivir rather than favipiravir because the saturation has already gone down. **In home quarantine and mildly symptomatic patients , antivirals should be started soon after diagnosis**.

Dr. Agam Vora:

Any patient presenting with Influenza like illness should be treated as COVID-19 unless proved otherwise. In mild to moderate case, pending results, empirically one can start favipiravir.

Dr. Raja Dhar:

Taking 'Informed consent' of the patient is important. Inform the patient or relative that you are giving the drug on an empirical basis for which it is not licensed. It should be done on a case to case basis rather than a blanket approach.

Case:

Subject F continued to worsen

- **On day 5: SpO2 80% on High-Flow Nasal Cannula(HFNC)**
- **HRCT worsening**
- **D-Dimer: 6500 ng/ml (45-500)**
- **S. Ferritin: 1350 ng/ml (30-400)**
- **CRP: 180 mg/l (1-5)**
- **IL-6: 350 pg/ml (<7)**

Q. Will you use remdesivir for Subject F? Dosage & duration? Side effects of the drug?

- **Dr. Raja Dhar:**

• **Remdesivir should definitely be started, if not yet started.** If patient was on favipiravir, one should stop favipirvair and start remdesivir instead.

• **The loading dose is 200 mg once a day followed by 100 mg once daily for duration of 5 – 10 days**. A small trial showed that there was not much difference for using it for 5 days versus 10 days.

- **Side effects are transaminitis, to be used with caution in patients with Creatinine clearance < 30, patients on hemodialysis.** Remdesivir trial excluded patients with Creatinine clearance < 30 and patients on hemodialysis. Therefore, data is not available in these patients. West Bengal Government has issued an Advisory not to use remdesivir in these patients. Therefore, the use has to be individualized, risks are less as compared to the benefits received from using this drug.

Q. Will you use immunomodulators for Subject F?
Which is your preference? Tocilizumab/Itolizumab/Omalizumab
When will you repeat the dose?

Dr. Randeep Guleria:

- If there is evidence that the patient is going into cytokine storm and there is worsening of the patient, you have to do risk-benefit analysis for giving anti-inflammatory, anti-IL6 drugs. **Tocilizumab can be given, it can be useful to some extent.**
- Data is controversial. Some studies have shown that it can be beneficial; some data showed that it may not be beneficial. There is no need to monitor IL-6 levels subsequently, IL-6 levels will be high or continue to rise. Some centres give multiple doses of tocilizumab just looking at the IL-6 levels. **You have to look at the clinical picture and wait for at**

least 48 hours and then decide whether further dose of tocilizumab is needed.

- **Itolizumab is an anti-CD6 drug, it has much stronger effect as far as immune system is concerned.** It blocks a number of cytokines like TNF alpha. Not much experience because the data is still not strong.
- RCT done to get DCGI clearance involved few patients, so it is not enough to say that this drug is effective. More data needed as far as itolizumab is concerned. We have to be careful because it **causes more immunosuppression and can lead to other issues in terms of secondary bacterial and fungal infections.**

Dr. Ketan Mehta:

Recently the Indian company has sent an official letter to all healthcare professionals. It says **'Tocilizumab is not approved for COVID-19 in India. In view of this, physicians should consider the risks and benefits of using Tocilizumab in unapproved indications.'**

Dr. Raja Dhar:

- Immunomodulators/monoclonal antibodies should not be given to patients on ventilator. If the patients are ventilated, chances of secondary infection, bacterial or fungal are far higher and there is an increased risk of mortality. Roche trial had 40% patients on

ventilator when the drug was administered. That might be a reason that the results were not very positive.Another important thing about itolizumab is **it has to be given very slowly as the risk of anaphylaxis is very high.** Patients on infusion can develop rigors, shivering, then the drug should be stopped and started again slowly.

- **Dr. Deepak Talwar:**

Patients are coming post COVID-19 with fungal and tubercular infection. There are cavities in the lung, fluid present, AFB positive, fungus positive. This is post tocilizumab. They already have fibrosis in the lungs. **Two to three weeks after discharge, patients are coming as post COVID fibrosis but the reason of worsening is also a super added infection as tocilizumab had been used extensively. When using tocilizumab, underlying tuberculosis or fungal infection is a really important aspect.**

- **Dr. Agam Vora:**

We have really overused tocilizumab. It is not required to that extent. Most patients do very well. **Only few patients develop real cytokine storm and require tocilizumab. In ICU, the chances of secondary infection with tocilizumab are very high.**

Dr. Randeep Guleria:

A very small percentage of patients require tocilizumab. **It has very limited role as far as COVID-19 is concerned.**

Q. Role of convalescent plasma/Immunoglobulins?

Dr. Agam Vora:

My experience is very limited.

Dr. Randeep Guleria:

- Convalescent plasma is old therapy, used for probably 100 years. It has been used for Spanish flu pandemic and recently Ebola.
- The initial trials did tend to show some benefit. Subsequent trial involving 103 patients did not show much benefit, but it was used very late even after 3 weeks.
- Everyone who has recovered may not have sufficient antibodies in his/her plasma to be called convalescent plasma. You may be giving plasma which may be having its benefit. You have to do an antibody titer, which is not done right now. We are just looking for the presence of antibodies and if antibodies are present we assume that they are in sufficient

titres and therefore it may be useful. Also, **it is useful to give it in the early phase, before 7th or 8th day, before body itself has produced antibodies.** There is a study which is preprint from Netherlands where they found that patients who had been given convalescent plasma had sufficient levels of antibodies on Day 10. There was no use in giving antibodies as they already had antibodies in sufficient quantities. It has limited role, **useful only in the early stages.**

- **It may be given in moderate disease going on to severe disease.** We need more data. The interim analysis done at our center, small study of 30 patients, did not point to any mortality benefit. A large trial completed by ICMR, 400 patients receiving convalescent plasma across the country, is not showing too much of a benefit. In this study however antibody titre was not done. So **it has limited role as of today.**
- With regards to **immunoglobulins**, more data is needed. There is **limited role**. There is no enough data to say that it should be standard of care.

Q. Role of anti-platelet vs anti-coagulant? Choice of agent? Which agent for which subject? (Father/Mother/Husband) Duration of therapy?

Dr. Deepak Talwar:

Both admitted patients will get Low Molecular Weight Heparin (LMWH)

Mother who had diabetes will get LMWH once a day. Father who is in ICU will get therapeutic dose of LMWH twice a day. They will continue to receive LMWH till they are mobile. The one who is in the ward hopefully recovers and goes home, doesn't go on enoxaparin or any or the LMWH. I would use prophylactic LMWH for the father who is in the ICU till he becomes mobile which may be even 1 -2 weeks after discharge.

Dr. Raja Dhar:

There is trial exploring the role of aspirin, but it is a negative trial. There is no head to head comparison trial between anti-platelet and anti-coagulant. **Patients having increasing titres of D-dimer or patients having single high D-dimer > 4000, might be sent on apixaban. Duration is 2 to 6 weeks.** Trials show a mortality benefit, even though the trials are small, not robust, observational trials.

Dr. Ketan Mehta:

One paper mentioned that apixaban had to be continued even on a OPD basis post discharge for a prolonged period of time.

Dr. Randeep Guleria:

At the time of discharge, do risk assessment using various scores of the risk of thromboembolic complications, DVT, thromboembolism for further decision. **Patients who have high D dimer, high risk of DVT in terms of immobility, obesity, should be given at least for 6 weeks and then take an assessment for further continuation.** 4 to 6 weeks is the standard duration which we would give to most of our patients.

Q. Your preference for delivery of O2? Role of positioning of the patient? Role of NIV?

Dr. Agam Vora:

- Oxygen delivery would depend on the level of hypoxia the patient has. Those who are mildly hypoxic will do extremely well on nasal prongs.
- If there is a refractory hypoxia, the pO2 does not rise by 10 when FiO2 is increased by 10%, you would give them a different delivery system – Venturi mask, reservoir bag, rebreathing mask, HFNC. If patient has increased work of breathing, or if patient has got CO2 retention, associated myocardial involvement and pulmonary edema, use non-invasive ventilator like BiPAP etc.
- **Prone positioning and steam inhalation is helpful.** All patients in my hospital get their own steam inhalation device and they are told to take steam inhalation twice daily. Whenever possible, when patients are not full stomach, they should lie down prone and probably that would open the dependent portion of the lung and improve oxygenation.
- Oxygen delivery depends on the kind of hypoxia they have. **There is a choice of nasal canula, masks, Venturi, reservoir bag, HFNC, and if required noninvasive ventilators.**

Dr. Raja Dhar:

Awake proning – meta-analysis results are really good. This is way of keeping people out of intensive care and in intensive care, preventing people from getting invasive mechanically ventilated. It is a great thing to do. It requires some time and persuasion from clinician, if managed to do well can prevent people from going to mechanical ventilation.

Dr. Randeep Guleria:

One has to really convince the patient. Show them the oximeter and tell them how it is working as many conscious patients get uncomfortable as far as proning is concerned.

Q. Patients who are already on following drugs have better outcome. What are your view points?
ACE-I, DPP-4 I (Gliptins), H2R blockers (ranitidine/ famotidine), Fenofibrate, Metformin, Colchicine

Dr. Ketan Mehta:

Patients who had hypertension and were taking ACE-I had a better outcome. Same was true for diabetic patients on gliptins, metformin, acid suppressing drugs, fenofibrate & colchicine.

ACE-I: Angiotensin-Converting-Enzyme Inhibitors DPP-4 I: Dipeptidyl Peptidase-4 Inhibitors H2R: Histamine 2 Receptor

Dr. Randeep Guleria:

These are just anecdotal reports or retrospective data. There are studies which have looked at all of these. Metformin has been used in large number of trials and it has shown benefit. It has also shown an anti-aging effect. Colchicine also has an immunomodulatory effect, it may decrease the inflammation. Therefore, they give it in patients who have mild to moderate disease. Some have found it to be useful. Again this is anecdotal, there is no robust data as far as any of these is concerned. More data is needed to say if they are beneficial.

Dr. Ketan Mehta:

The message is not to recommend these drugs, but there is no need to change medicines in patients already taking these drugs.

Q. Role of miscellaneous compounds?

1) Mycobacterium W 2) Nattokinase
3) L-arginine 4) NAC 5) Picnovit/ Pine bark extract

Dr. Agam Vora:

All these molecules have some role to play in small specific group of patients which we require to identify. They all have immunomodulating role. Theoretically, they all have immunomodulating activity, but we do not have robust data talking about it. At this stage I would refrain using it on a community level.

Q. Role of VIP (aviptadil) – RLF 100?
Role of Laser treatment in COVID-19 pneumonia?

Dr. Raja Dhar:

The data is preliminary. These are 'proof-of-concept' studies which show that they might actually work. Human trials are awaited. At this stage, there is no indication to use in COVID-19.

NAC: N-Acetyl Cysteine VIP: Vasoactive Intestinal Peptide