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CASE REPORT CORONA EXPERIENCE

COVID-19 cytokine storm treated successfully: As reported by two doctor victims

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Abstract

Covid-19 worldwide pandemic struck India when 1st case was reported on Jan30th 2020. Amidst the great challenge faced by treating physicians, to cure their patients, with continuously evolving management strategies, some also got infected, despite of all preventive measures taken.

We present here two such cases where the doctors themselves have narrated their course of disease and management plus back up support.

Proper strategic management of the illness according to WHO and ICMR protocols, along with good physicians' cover 24/7 was the hallmark of good outcome.

Timely identification and immediate treatment of cytokine storm helped in allaying the worsening of pulmonary and other systemic effects of the disease.

Key words: Covid-19; Oxygen saturation; Cytokine storm; Interleukin-6, Tocilizumab

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1. Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has high rates of infectivity and pathogenicity. The overproduction of early response proinflammatory cytokines (tumour necrosis factor [TNF], IL-6, and IL-1β) results in what has been described as a cytokine storm, leading to an increased risk of vascular hyperpermeability, multiorgan failure, and eventually death when the high cytokine concentrations are unabated over time.[1] In vitro cell experiments show that delayed release of cytokines and chemokines occurs in respiratory epithelial cells, dendritic cells (DCs), and macrophages at the early stage of SARS-CoV infection.[2] Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality.[3] Therefore, healthcare workers were not spared in spite of taking all preventive measures. Tocilizumab can be used to treat cytokine storm of the COVID-19 patients that targets IL-6R. It is a humanized monoclonal antibody (hmAB) and also is an antagonist IL-6R. IL-6 level is significantly increased in serum in COVID-19 infected severe patients.[4] It causes impaired oxygen diffusion leading to respiratory fatigue and then failure. Therefore, Tocilizumab may be used as a treatment option. Doctor community accordingly also paid heavier toll regarding doctors getting infected, as well as there were appx more than 200 deaths among doctors reported from India.[5] We present here two cases of

doctors, who got infected and their course of disease and management strategy is narrated herewith in their own words.

2. CASE Report 1: Dr. Ram Bihade

I have been treated for COVID-19 pneumonia with cytokine storm. Today I was discharged home after 22 days. I share my experience with the readers.

On 23rd May 2020, evening, I developed high grade fever and severe headache. Five days earlier, I had attended a patient in OPD at Akola GMC, who came after giving his swab in COVID OPD. I examined him with full precautions, e.g., gloves, N95 mask and face shield. Possibly he was the source of my infection, as after that I quarantined myself at home with no outside contact till symptoms appeared.

I contacted COVID OPD and a throat swab was taken on 24th May. I was already taking chloroquine prophylaxis. I started on oseltamivir, azithromycin and antipyretics. Fever was above 102 °F.

On the evening of 26th May, my report came positive and I was advised to get admitted in ICU ward side room. Around 9 pm I was admitted. At that time private medical institutions were not allowed to admit COVID patients.

First set of investigations pointed out that the infection might be relatively uncomplicated one. Labs were normal, e.g., CBC, CRP, ferritin, D. Dimer, procalcitonin, quantitative TROP-I), except LDH at 577 units per liter (U/L) (normal: 140 U/L to 280 U/L). IL 6 levels could not be done.

I was started on antibiotics, vitamin C and zinc.

Fever persisted on 27th May, ranging from 102 to 104 °F. IV paracetamol would just act for short time. I had fatigue, but not hindering my daily activities. Oral paracetamol did not work.

I monitored my temperature myself because the non-touch temperature readers showed significantly lower values than my personal thermometer.

On 28th morning I developed persistent fever and tachycardia and even more fatigue. Saturation was 98% on room air. I was put on piperacillin (4000 mg) + tazobactam (500 mg) TDS, methyl prednisone 40 mg BID and parenteral vitamin C. It was made sure that I received all the drugs in timely manner. Blood reports on 28th showed D-dimer of more than 1000 and CRP of 10 (normal = 6). Serum ferritin was normal. So LMWH injections were started.

On 29th, fever spikes reduced and the requirement of paracetamol went down. Maximum temperature was still 101 °F, tachycardia (at 110/min) was still there. I felt symptomatically better probably, due to reduced fever as a result of corticosteroids. I even walked for 30 min without feeling much fatigue.

On 30th, I woke up early with a fever of 102.5 °F. I realized I was sicker. Fatigue was back. Oxygen saturation 93-96%. Intermittent oxygen was started. It was day 8 and the time when things turn worse in symptomatic Covid. I was put on bed rest. Piperacillin + tazobactam replaced with inj. meropenem. Fatigue was so bad that going to washroom felt like 100-meter dash. I could feel my strength being doomed. I reduced my activities to conserve energy. Increased the duration of proning and followed CARP protocol. Blood reports showed ferritin at 310 (upper normal for men 276) and D-dimer reduced to 510. Neutrophil to lymphocyte ratio was 4:1, which was 3:1 earlier.

My NEWS score (National early warning score) on admission was 2; jumped to 5 in one day. It might be the start of cytokine storm and I was told I might require tocilizumab. The drug was very difficult to get and I did not want Ulinastatin which was not as robust as tocilizumab.

On 31st, my clinical condition deteriorated further. I couldn't go to washroom. I felt I would pass out. Checked oxygen saturation it was 85% at room air, continuous oxygen was started. Fatigue was so severe that I was hardly able to get up from my bed. Oxygen demand had increased significantly to about 10 L/min now. I felt clinically it was cytokine storm and I needed tocilizumab, so messaged my treating physician. I could barely type texts. Doctors Zubin and others tried to arrange tocilizumab, but in vain.

The day was very eventful even though my clinical parameters and tests were not significantly deranged. Most of them mistook my physical weakness as my mental weakness. The truth is my mind was clear as ever probably sharper. Was I afraid? - yes, I was! There was fear of death, which I believe is the most powerful impulse to human spirit which helps us to

fight. But I was not depressed at all. There were talks of shifting me to Nagpur /Pune/ Aurangabad, and I asked to do so only if tocilizumab was available there or it would be useless.

Anyway, continuing with the story my sample for IL-6 was sent to Mumbai before first dose of tocilizumab. Results would arrive on 5th or 6th June.

It was the first time that tocilizumab was being administered in GMC, practical experience with tocilizumab was next to nothing. Ten minutes into the dose I had a reaction, with full rigors and difficulty in breathing. I signaled one of the patients to call the doctor. Doctor came immediately, managed it and after sometime I was out of the woods. Thanks for the timely treatment, rest of the infusion went smooth.

On 1st June, fever reduced, fatigue and tachycardia persisted with wide variations in pulse with posture change. CRP was raised. LDH, ferritin, D-dimer were normal. Oxygen requirement had gone up to 15 L/min. I received second dose of tocilizumab 12 hours after the first dose. With a bad experience with first dose, all were fully alert.

2nd June, third dose of tocilizumab was decided to be given judging from the clinical picture. Oxygen requirement were still 15 L/min.

3rd June: Fever was gone. Fatigue was slightly reduced. My wife had her second throat swab positive and even though she had mild symptoms, she decided to get admitted with me. This really turned out to be a blessing in disguise for me.

4th June: I felt really better. Had no fever, no tachycardia, and comparatively less fatigue. The only problem left was the oxygen requirement. I was put on CPAP support with 70% FiO_2.

5th June: IL-6 levels arrived with 400 times increase of the normal value. I thanked Almighty that I received tocilizumab in time or everything could have been a disaster.

Repeat throat swab came negative on 9th. The oxygen requirement went down steadily with spirometry, deep breathing exercises and CARP protocol. Both of us took discharge from GMC Akola on 12th June.

I shifted to Ozone Hospital, as there was still minimal oxygen requirement; stayed there for three days and took discharge when I was able to maintain steady SpO_2 at room air with routine activities. Took a break of one month for recuperation, pulmonary rehabilitation and increase in exercise tolerance.

Some lessons I learnt;

- Never ignore red flags and clinical condition of the patient. Laboratory investigation reports cannot replace clinical judgement.
- ARDS can be avoided with timely identification of cytokine storm.
- NEWS scoring system can help to objectify clinical deterioration compulsorily should be used in every patient
- IL-6 levels cannot be substituted by other markers.
- Tocilizumab can work wonders, if received timely and is not contraindicated. Due to short supply, hospital should have it in their stock.
- Never feel shy / embarrassed to ask for help. There is plenty of help available from medical fraternity.
- What doesn't kill you makes you mentally stronger.

3. CASE Report 2: Dr. Nizamuddin Kotwal

I was doing my regular clinic along with my wife Dr Nisha, a gynecologist at Solapur.

On night of 5th June 2020, my wife had mild flu like symptoms with body ache. Immediately, we both isolated ourselves. She took medication. She developed high grade fever on 6th and 7th, which gradually reduced by 8th.

I had only body aches on 5th June, only to have severe myalgia by 8th and raging fever of 101-103.4 ^{0}F with chills and rigors. On 11th, I had severe nausea and vomiting. I was unable to tolerate even a sip of water; that is when we got admitted. My oxygen saturation remained above 95%.

On 12th, I was shifted to Pune where a throat swab was taken. Feeling uncomfortable we returned to Solapur.

On 13th, I felt better. However, I got readmitted as a prophylactic measure. As expected, both my wife and I turned out to be COVID positive. I was put on inj. enoxaparin 40 mg OD (LMWH) as my D-dimer was

800 (reference value < 250 ng/mL, or < 0.4 mcg/mL) and inj. methylprednisolone 40 mg BD as my ferritin and CRP were high. My wife and I were admitted together and our discharge was due on 20th of June. During our stay Dr Vishal Gore treated me really well.

On 17th I had a spike of fever (100 °F), relieved by tab paracetamol. I maintained saturation at 94% off O_2. I was unable to sleep in supine position; with adjustments I finally fell asleep at 90 degrees.

On 18th, I developed high-grade fever (101-102 °F). My inflammatory markers were sent. All the markers were in thousands. To my horror, it was the dreaded ‘cytokine storm’.

My chest x-ray was normal and I still maintained 96% saturation on 4 L oxygen and started feeling comfortable. My wife monitored my stats and realized that slowly the baseline was shifting from 94% downwards. Finally, at 2 AM it was 88%! She called Dr. Vishal who sat by my side till 4 AM to monitor me personally. I had severe chest pain, so was shifted to ICU, my ECG was normal. I was uncomfortable and breathless in all positions. I was given inj. tocilizumab which brought my saturation up to 90% but the discomfort persisted.

On 19th June, my high-resolution computed tomography (HRCT) showed >70% lung involvement with ground glass opacities and I developed asynchronous breathing. This was the most terrifying experience of my life. I couldn’t breathe, I couldn’t think and all I could see was my family all alone without me. With the little strength I could muster, I took my wife’s hand and shared my term insurance policy details with her, told her to look after our lovely children (son Hussain and daughter Mariya) and my elderly parents. I asked her to stay strong in life and take all further decisions regarding my treatment.

She called all of our doctor friends. All these wonderful people stood as a rock-solid support system and decided to shift me to Pune Sahyadri Hospital. We feared possibility of some problems during transit and started reviewing the possible complications.

At 12 pm while my friends and my wife were deciding the best course of action, my physician called my other friends to evaluate me. At this time, high-flow nasal oxygen therapy (HFNO) was not available there, but Dr Yogesh Rathod arranged it by the next day. I was shifted to Yashodhara Hospital ICU at 6 pm.

At Yashodhara my saturation dropped to 85% off oxygen, so I was put on BIPAP. My breathing improved, but I still couldn’t sleep.

On 20th at 5 pm, I was put on newly arrived HFNO machine at 20 L with humidifier. With this arrangement, I was maintaining saturation at 97% and pulse rate of 80-90 beats/min, and finally got a restful sleep after 4 nights. Saturation improved marginally to 88% off oxygen.

On 21st, my HFNO was reduced to 15 L and I was shifted to a room. COVID Awake Repositioning / Proning Protocol (CARP) was started; initially I couldn’t lay down in < 60°. With support I started prone ventilation by nightfall. I could now eat semisolid food after 4 days and control respiration and swallowing.

On 22nd, HFNO was tapered down to 10 L. I could perform CARP effortlessly, eat solid food, use washroom without assistance and breathe freely.

On 23rd, oxygen was stopped and I was put on 10 L high flow (on HFNO machine) atmospheric oxygen (21% PaO2). I now maintained 92-93% saturation and had no breathlessness.

On 24th, the HFNO machine was disconnected. On 25th, by God’s grace I managed to walk for 30 min without fall in saturation. On 26th, I was discharged from the hospital with 95% saturation.

In my life changing journey, I would like to remember everyone who stood by me. My wife Nisha, a pillar of strength, and all my physicians, friends and family. I thank God for giving me a new life.

Things to remember: If you have symptoms get tested. Don’t panic. ISOLATE yourself. Consult a covid doctor, even if you are a doctor yourself. Do a pre disease survey and prepare your strategy beforehand. Keep phone numbers handy. Thermometer and pulse oximeter are a must in every house. Know your baseline O2 saturation and HR. Keep well hydrated. Keep eating even with anosmia. Up to 14 days are very critical. Seek help immediately. Physiotherapy, Spirometry and yoga help. Keep a positive mindset. Pray and get treated. OPD is where we are casual and most susceptible, I request all of you to please use PPE in OPD.

4. Discussion

The spread of COVID-19 overwhelmed the healthcare systems of many countries and even crashed the fragile healthcare systems of some. Although the situation in each country is different, health workers play a critical role in the fight against COVID-19.

India has paid a heavy toll by loss of appx.200 doctors. WHO Corona virus dashboard showed total 255,41380 cases, out of which India had 376,9523 cases. Total global deaths reported on 2nd Sept.2020 were 852000, out of which India 66333 deaths. India reported highest no. of new cases viz.78,357in last 24hrs.Spread in India was mainly in clusters and not community transmission.

The two doctors under discussion are 35 and 38 yrs. old, from state of Maharashtra, which was badly affected by Covid-19. Both caught the infection as suspected from outpatient department. Both isolated themselves at home initially, but with advent of symptoms, they had to get tested and when proved positive, had to get admitted to hospital.

One of them was on chloroquine prophylaxis. Common symptoms in both were high grade fever, fatigue, nausea and vomiting. Both had fall in oxygen saturations and were given supplemental oxygen. HFNO (High Frequency Nasal Oxygen) was used in one and CPAP in other. Both had cytokine storm which was timely recognized and treated with tocilizumab and prednisolone.

The symptomatology and treatment strategy though followed according to WHO and ICMR guidelines in the two self-narrated stories of doctors shows the best use of the guidelines of treatment as well as taking into account the resources and backup services and availability and timely dispensing of drugs with the fellow doctors' vigilant cooperation, which led to their good outcome.

5. Conclusion

The early detection of cytokine storm in COVID 19 patients, could allow for affective management plan which would positively impact recovery and in turn reduce morbidity and mortality. Tocilizumab, the IL - 6 antagonist could have immense impact in controlling the effects of cytokine storm and maybe the factor decreasing respiratory compromise, thus reducing the need for ventilatory support in COVID 19 patients. The backup support provided by fellow peers and colleagues may very well be the pivotal factor for successful management and recovery of doctors affected.

6. Conflict of interest

None declared by the authors

7. Authors' contribution

MK, RH- Drafted the case report, had liaison with the victims and urged them to document their personal experience

NK, RB- Both of these doctors fell victim to Covid-19, and survived cytokine storm. This is their first-hand personal story as quoted to RH.

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