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Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth Buster

Round Table Expert Zoom Meeting on "Recovery is the Rule in COVID-19 and Death is an Exception"

4th July, 2020 (11 am-12 noon)

Participants: Dr KK Aggarwal, Dr Shashank Joshi, Prof Mahesh Verma, Dr Ashok Gupta, Dr Suneela Garg, Dr JA Jayalal, Dr Jayakrishnan AV, Dr Alex Thomas, Dr Shiv K Harti, Vaidya Sushil Dubey, Mrs Upasana Arora, Dr K Kalra, Ms Ira Gupta, Dr S Sharma

Key Points from the Discussion

- Timely action can save lives as most cases are mild; few are moderate and less than 5% are serious.
- Death rate is reducing as we are now able to better manage cases.
- In all patients who have loss of smell/taste, recovery is the rule and mortality is an exception. Analysis of 100 patients with loss of smell/taste showed that none needed oxygen or ventilator or hospitalization. It occurred more often in males, at any age and recovery is the rule within 4 weeks.
- Recovery is the rule means that the disease is salvageable at every step. It does not mean that mortality is zero.
- After 9 days, the virus becomes nonreplicative and after 9 days, the illness is a post-COVID (coronavirus disease) complication.
- Day 1 is the day when any of the symptom/s recognized by the Centers for Disease Control and Prevention/Ministry of Health and Family Welfare (CDC/MoHFW) guidelines such as fever, throat irritation, subconjuctival hemorrhage, rash, diarrhea, headache, calf pain, etc., develop; test may or may not be positive.
- Post-COVID inflammation is very common. It can be in the form of persistent fever/sore throat/bronchitis/diarrhea/cystitis/exertional tachycardia.
- Doctors have high viral load because of repeated exposure and they have more hypercoagulable state. So, if all healthcare workers (HCWs) are given anticoagulant + short course of steroids, even in mild cases, recovery is the rule.
- In non-HCW group of patients, if there are signs of chest congestion on Day 3-4, do an immediate chest CT scan and give 10-day course of steroids, antiviral and anticoagulant; then recovery should be the rule and death an exception.
- Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) may be positive for up to 40 days; this does not mean that the virus is culturable. The virus is culturable for only 9 days; after 9 days, the virus is present but is non-culturable. This data is available for patients who are not on ventilator.
- If any illness is developed during the 9 days, then the post-COVID illness (post-COVID inflammatory state) may last for up to 6 weeks.
- A delayed cytokine storm, which occurs between Day 14 and 18, has been observed in Mumbai. A 6-minute walk test is now mandatory at the time of discharge to look for drop in oxygen saturation. This is a valid marker for delayed cytokine storm. Give 5-10 days of low-molecular-weight heparin (LMWH)/oral anticoagulant and small dose of statin at the time of discharge, especially to those who have been in hospital for >28 days and are >55 years of age. This can reduce mortality.
- Initially, steroids were given only in serious cases, but now their indication has also shifted to moderately severe cases. And the time may well come when steroids may become mandatory in all patients starting from Day 3. Timely steroids can prevent secondary cytokine crisis.
- Capacity building, not just of HCWs but also RWAs, etc., as many patients are in home care; issues like stigma and discrimination also need to be addressed. The word "contact" needs to be eliminated as it is a type of stigma.
- Indian vaccine is a live attenuated vaccine (Bharat Biotech); Moderna vaccine is mRNA vaccine; all vaccines have different technologies. Three things to be detected when a vaccine is given: Cellular antibodies, humoral protection and non-specific immunity building (innate immunity). By 15th August, we may only be able to tell whether

antibodies are produced or not. Since this is a live attenuated virus, will there be a delayed response (cytokine crisis), we do not know.

- Isolate for 9 days, quarantine for 5 days and then monitoring with rest for next 2 weeks. Monitoring means that the person is not contagious, but is still likely to get secondary complications.
- Plasma therapy is effective if given within first 7 days of illness; plasma should be donated between 28 and 40 days.

Healthcare Workers with Appropriate PPE Don't Get COVID-19

- Healthcare workers (HCWs) with appropriate PPE (protective suits, masks, gloves, goggles, face shields and gowns) don't develop COVID-19 symptoms or test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as per a Chinese study.
- The study examined data on 116 doctors and 304 nurses who were deployed to Wuhan, China, for 6-8 weeks from January 24, 2020 to April 7, 2020. They were all involved in aerosol-generating procedures, and were provided with appropriate PPE to care for patients with COVID-19.
- Participants worked 4- to 6-hour shifts over an average of 5.4 days a week, and spent an average of 16.2 hours weekly working in intensive care units (ICU).
- None of them reported COVID-19 symptoms when they were deployed to hospitals in Wuhan. After they returned home, all tested negative for SARS-CoV-2 specific nucleic acids and IgG or IgM antibodies.
- In Wuhan, most of the affected health professionals became infected in the early phase of the outbreak due to a lack of appropriate PPE.
- More than 80% of patients required critical care and 10-15% received mechanical ventilation.
- All participants received similar PPE and proper training to work in the ICU, regular wards and for cases involving aerosol-generating procedures (N95 respirator masks, medical suits, isolation gowns, aprons, gloves, eye protection and hair coverings. In areas with no COVID-19 contact, workers wore surgical masks).
- All of the study participants performed at least one procedure generating aerosols, including tracheal intubation, noninvasive mechanical ventilation, gastric intubation, sputum aspiration, aerosol inhalation, tracheostomy and throat swab collection.
- Out of hospital, they wore masks in public, followed strict social distancing rules and stayed in designated hotels.

(Source: The BMJ, online June 10, 2020.)

Predicting Factors for Pulmonary Embolism in Non-critically Ill COVID-19 Patients – D-dimer >5,000

A Spanish study published in the *Journal of Thrombosis and Thrombolysis* has reported a high rate of pulmonary embolism (PE) in non-critically ill hospitalized patients with COVID-19 despite the use of standard thromboprophylaxis. B Mestre-Gómez, Internal Medicine Department, Infanta Leonor University Hospital, Madrid, Spain and colleagues stated that they had found 29 patients with established PE and COVID-19 pneumonia out of 91 CTPA (computed tomography pulmonary angiography) tests performed among 452 patients admitted over the study period. This points to an incidence of 6.4% in a medical ward and one-third of positive CTPA despite prophylactic doses of LMWH.

Investigators further stated that an increase in D-dimer levels is a potential predictor of PE, with a best cut-off point of >5,000 μg/dL.

The single cohort, longitudinal study assessed patients admitted with COVID-19 diagnosis to the Internal Medicine Department of a secondary hospital in Madrid from March 30 through April 12, 2020. A retrospective review of 452 electronic medical records was done, to assess the cumulative incidence of PE, and associated risk factors. Ninety-one patients who underwent a multidetector CTPA during conventional hospitalization were included in the study.

Of the 91 CT scans, 29 patients (31.9%) were diagnosed with acute PE, while the cumulative incidence over the entire cohort was 6.4% (29/452 patients). Among the PE patients, 23 were found to have COVID-19 infection via RT-PCR positive tests, and 6 had positive CT scans and negative RT-PCR.

Among the PE patients, 72% (21/29) were male and the median age was 65 years (IQ 1-3: 56-73), while median body mass index was 28.8 kg/m^2 (IQ 1-3: 26.8-31.8). Median plasma D-dimer peak was 14,480 μg/dL (IQ 1-3: 5,540-33,170 μg/dL), median platelet counts 137×10^3 (IQ 1-3: 248-260 $\times 10^3$), median C-reactive protein 110.6 mg/dL (Q1-3: 40-193) and median ferritin 829 ng/mL (Q1-3: 387-1272). There appeared to be no associated

coagulopathy, with a prothrombin time of 12.5 seconds (Q1-Q3: 11.9-13.5). Most of the PE patients were given LMWH (79.3%; 23/29) at prophylactic doses at the time of diagnosis of PE.

Nearly 51.7% of PE cases were bilateral (15/29 patients) and 48.3% unilateral. Most PEs were noted in a peripheral location in segmental and subsegmental arteries (68.9%, 20/29 patients) and 31.0% (9/29 patients) in a central location (main and lobar arteries).

It was noted that D-dimer peak was significantly elevated in the PE patients (median 14,480 μg/dL, IQR 5,540-33,170) compared to patients without PE (7,230 μg/dL, IQR 2,100-16,415; p = 0.03).

A multivariate analysis of patients subjected to a CTPA suggested that plasma D-dimer peak independently predicted PE with a best cut-off point of >5,000 μg/dL (OR 3.77; IC95% (1.18-12.16), p = 0.03).

There were statistically significant differences between the two groups for history of dyslipidemia (10.7%, [3/29] in PE patients vs. 40.3% (25/62) in non-PE patients, p = 0.003), and for history of autoimmune disease (10.7% [3/29] vs. 0% [0/62], p = 0.03).

Investigators stated that the history of dyslipidemia appeared to be a protector factor for PE in the multivariate analysis. Patients who did not have this cardiovascular risk in their records, were found to have a nine times increased risk for PE compared to those with dyslipidemia (OR 9.06; IC95% (1.88-43.60). It seems possible that patients previously treated with statins had a potential benefit either by their immunomodulatory action or by preventing cardiovascular damage.

No statistical differences were noted in either mortality or admission to the ICU between the PE and non-PE groups in this cohort of non-critically ill COVID-19 patients.

The absence of classic risk factor for venous thromboembolism - advanced age, history of thrombosis, thrombophilia, cancer and ICU admission - and the peripherical localization of PE suggest microthrombosis *in situ*. Wells index does not seem to be accurate to predict PE in such a challenging context, according to the authors.

Additionally, there was no difference in severity of pneumonia by CURB-65 score. Furthermore, no statistical difference was evident in inflammation parameters (high in both groups), treatment or need of noninvasive ventilation; however, the figures are higher for non-PE group.

The actual presence of PE on CT was not found to be linked with mortality in this small sample.

(Source: DG Alerts; Journal of Thrombosis and Thrombolysis)

Minutes of Virtual Meeting of CMAAO NMAs on "Managing Fever"

4th July, 2020, Saturday (9:30 am-10:30 am)

Participants

***Member NMAs*:** Dr KK Aggarwal, President-CMAAO; Dr Yeh Woei Chong, Singapore Chair CMAAO; Dr Thirunavukarasu Rajoo, Hon. General Secretary-Malaysian Medical Association; Dr Alvin Yee-Shing Chan, Hong Kong; Dr Marie Uzawa Urabe, Japan; Dr Md Jamaluddin Chowdhury, Bangladesh; Dr Qaisar Sajjad, Pakistan; Prof Ashraf Nizami, Pakistan; Dr Prakash Budhathoky, Nepal

***Invitees*:** Dr Russell D'Souza, UNESCO Chair in Bioethics, Australia; Dr Sanchita Sharma, Editor-IJCP Group

Key Points from the Discussion

Dr KK Aggarwal shared his observations of about 100 patients with loss of taste and/or smell: They did not need hospitalization, none developed pneumonia, recovered in less than 4 weeks, more in men, none needed oxygen, about 50% recovered without treatment. It was the only presentation in many patients. Bitter and sour tastes and sour (lime) smell are retained.

After 9 days, the virus becomes non-replicative; there is no evidence that the virus is culturable after 9 days except for cases who were on ventilator. Antigen can remain positive for up to 40 days. There is also no evidence to date that a culturable virus is positive again.

India is now doing rapid antigen test. If antigen test is negative, do RT-PCR. If antigen test is positive, then this is considered positive. Antibody test (COVID-specific IgG) is done after 14 days.

If antigen is positive and COVID-specific IgG antibody is negative, this is resurgence of old infection. If COVID-specific IgG antibodies are present and RT-PCR is positive, look for other causes of fever.

The patient who comes after 9 days presents with post-COVID sequelae. These patients have persistent systemic inflammation. The commonest presentation is post-COVID fever (low grade <100.4, does not respond to paracetamol, responds to anti-inflammatory drugs like mefenamic acid, naproxen, nimesulide and indomethacin). Other presentations may be post-COVID bronchitis/sore throat/diarrhea/cystitis/exertional tachycardia.

If less than 9 days, critical days are Day 3, 4 and 5; if patient has chest congestion during these days, this is suggestive of pneumonia. A CT scan will show the pneumonia.

If at the onset of pneumonia, patient is given dexamethasone 6 mg × 10 days, statin and oral anticoagulant (rivaroxaban) × 40 days and antiviral, mortality may be reduced.

Secondary sudden death (after Day 14) may occur even after a month of recovery. Hypercoagulable state can last for up to 40 days.

Pakistan Update

- Patients have post-COVID problems, but not too much. Patients usually have fever, weakness lasting up to 2-3 weeks, loss of smell/taste × 4-5 days.
- Patients are advised to avoid exertion and take rest, hydration, multivitamins, vitamin D and balanced diet.
- If post-COVID patients complain of body pain or throat pain, ibuprofen or diclofenac has good response.

Bangladesh Update

- The number of cases are increasing; the number of deaths also increasing.
- Many hospital beds are vacant; this may be due to people taking oxygen at home. So, such cases are probably not coming to the hospital.

Malaysia Update

- Less than 100 patients in hospital; death rate <1.4%.
- All travelers coming into Malaysia are tested (antigen test) at the airport, they are required to download an App on their phones and undergo 14-day home quarantine. On the 13th day, they can go to GP clinic and undergo antibody test. On Day 14, they go to district health officer and report.
- No post-COVID fever reported so far.

Nepal Update

- Post-COVID fever is rare; there are 2 cases who recovered and were discharged and then presented with fever. They tested positive (RT-PCR).

Japan Update

- There are post-COVID fever cases, but the number is not so high.

Hong Kong Update

- There are about 1,200 cases, mostly imported cases; local community cases are only a small minority.
- Number of daily tests is around 3,000 and trying to increase number of testing.
- Relaxation of regulations of limiting public gatherings.

Australia Update

- A judicial inquiry is being held in the state of Victoria (Melbourne) following protocol breach by some of the security looking after international quarantined persons lodged in hotel.
- Rest of Australia is opened up; lockdown (phase 3) only in Victoria. In 10 days, cases have increased to more than 500. Only 5 are in intensive care. Army has been called in.
- Saliva test for coronavirus has been started in Melbourne in hotspots; it is not as specific as nasopharyngeal swab.

COVID Vaccine

Various parts of the virus are being used to manufacture the vaccine. Also, there are different ways to produce vaccine: Killed virus, live attenuated virus (India, phase 1 trial), mRNA vaccine (Moderna), spike protein (Oxford), VLP platform, conjugate vaccine, membrane and envelope vaccine. We have no idea which vaccine will succeed. We have to be guardedly optimistic about the vaccine. There are many unanswered questions such as:

- Will the vaccine produce cellular or humoral antibody? Vaccine may produce cellular reaction, but may not prevent cytokine crisis.
- Will they produce antibodies which are safe?
- Will they be able to prevent thromboinflammation?
- Will the effect of the vaccine be long-lasting or not?
- The mRNA can go into every cell of the body; this may be a cause for concern.

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