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Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth Buster

COVID-19 Update

- An analysis of primary human lung cells that were infected in the lab with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) revealed how the cells accumulated large amounts of lipid droplets. Following infection, the lung proteins down-regulate the ability of lung cells to burn carbohydrates and fatty acids. Lung cells cannot hold fat. This could possibly explain some of the severe damage that is done to the lungs of patients with coronavirus disease 2019 (COVID-19). The virus depends on glucose uptake, cholesterol production and fatty acid oxidation. Additional research is needed on the cholesterol drug fenofibrate before clinical trials can start.
- The antihistamine cloperastine, mostly sold in Japan, tends to block glucose uptake in lung cells and has shown some effect in fighting COVID-19.
- Moderna's experimental COVID-19 vaccine led to a strong immune response and provided protection against infection in monkey study. The vaccine, mRNA-1273, when given to non-human primates provided protection against infection in the lungs and nose, and prevented pulmonary disease. Results of the study were published in the *New England Journal of Medicine*.

  It appears to be an improvement over the results of AstraZeneca's COVID-19 vaccine in a similar study. This study included 24 monkeys, where Moderna tested 10 μg or 100 μg of the vaccine against no treatment.

  Both doses were found to be effective in protecting against viral replication in the lungs and lung inflammation. The larger dose also protected against viral replication in the nose of the animals.
- A vaccine being developed by AstraZeneca and Oxford University is among the most advanced in human trials. In a similar animal study, this vaccine also appeared to prevent damage to the lungs and prevent the virus from replicating. However, the virus actively replicated in the nose.

SARS-CoV-2 Virus Shows Little Variability Regardless of Mutations

SARS-CoV-2 mutation rate continues to below. Strain G seems to be the most widespread across Europe and Italy. The L strain from Wuhan appears to be disappearing slowly. These mutations do not seem to influence the process of developing effective vaccines.

SARS-CoV-2 has been reported to present at least six strains. Despite the mutations, the virus has demonstrated little variability, which is a positive news for the researchers working on a viable vaccine.

These results come from the most extensive study ever done on SARS-CoV-2 sequencing.

Investigators at the University of Bologna analyzed 48,635 coronavirus genomes, isolated by researchers in labs across the world. Investigators then mapped the spread and the mutations of the virus during its journey to all continents. The study was published in the journal *Frontiers in Microbiology*.

The first results are encouraging as they demonstrated that the coronavirus presents little variability, with about seven mutations per sample.

The variability rate of common influenza is more than double.

Federico Giorgi, a researcher at Unibo and study coordinator explained that the SARS-CoV-2 coronavirus seems optimized to affect human beings, thus explaining its low evolutionary change. This would mean that the treatments that are being developing, including a vaccine, might prove to be effective against all the virus strains.

There are six strains of coronavirus presently:

- The original - **the L strain** – that appeared in Wuhan in December 2019.
- Its first mutation - **the S strain** – that appeared at the beginning of 2020.
- **Strains V and G** – since mid-January 2020.

Strain G has been the most widespread till date. It mutated into **strains GR and GH** at the end of February 2020.

Strain G and its related strains GR and GH have been the most widespread till date, and account for 74% of all gene sequences that were analyzed in the study. These strains present four mutations, two of which can change the sequence of the RNA polymerase and Spike proteins of the virus. This could possibly have a role in facilitating the spread of the virus.

Strains G and GR seem to be most widespread across Europe and Italy. GH strain appears close to nonexistence in Italy, but is more widespread in France and Germany. This possibly validates the effectiveness of containment methods.

The most widespread strain in North America is GH, while GR strain occurs more frequently in South America.

In Asia, where the L strain initially appeared, the spread of G, GH and GR strains is gaining pace.

These strains came to Asia at the beginning of March, over a month after their spread in Europe.

On a global level, strains G, GH and GR are increasing. Strain S exists in some restricted areas in the US and Spain. L and V strains seem to be gradually disappearing. (*Science Daily*)

Minutes of Virtual Meeting of CMAAO NMAs on "Asian Countries Update – Part 1"

1st August, 2020 (9.30 am-10.30 am)

Participants: Member NMAs

Dr KK Aggarwal, President-CMAAO; Dr Yeh Woei Chong, Singapore Chair-CMAAO; Dr Marthanda Pillai, Member-World Medical Council; Dr Alvin Yee-Shing Chan, Hong Kong; Dr Subramaniam Muniandy, Malaysia; Dr Marie Uzawa Urabe, Japan; Dr Ashraf Nizami, Pakistan; Dr Prakash Budhathoky, Nepal

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

Dr Marthanda Pillai spoke about COVID situation in the Gulf countries. Dr KK Aggarwal analyzed the COVID data in South Asia and Dr Yeh Woei Chong gave an update on COVID in China, South Korea and Singapore. Dr Alvin Yee-Shing Chan spoke on the current scenario of COVID in Hong Kong.

COVID in Gulf countries

Dr Marthanda Pillai

- Many of the Gulf countries have been proactive in their response to COVID-19, launching tremendous efforts to control the infection prior to detecting the first case.
- Iran was the first country to be affected; it continues to be a hotspot.
- Saudi Arabia: Spread from Iran; disease detected in Jan/Feb, quick to implement measures to control the infection.
- UAE reported four cases on 29th January. Subsequently, Bahrain, Kuwait, Oman, Iraq and Qatar reported their first case in late February. These cases were either Iranians or citizens of Gulf countries who had recently visited Iran.
- Lockdown has been implemented, schools/religious places have been closed, no public transport in operation.
- There is a good system of testing.
- The entire treatment is free, especially COVID-19 treatment, for all citizens.
- Overall, total cases are around 2.3 lakh; the cure rate is around 45-50%. Mortality is less than 1%, except in Iran, where mortality is 3.2%.
- Non-COVID patients are restricted; e-prescriptions are being given, which has helped to control the infection.
- Restrictions are in place; there is no international travel except chartered flights for people who wish to go back to their country of origin. Their status is checked.
- The status of these countries has an indirect impact on the situation in our countries.

COVID-19 in South Asia

Dr KK Aggarwal

- The South Asian region includes 8 countries: Afghanistan, Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan and Sri Lanka.
- If the population density is more, the number of cases will be more in the first wave. If density is more than 1,000, the number of cases is higher. Among the 5 countries, Bangladesh is the most densely-populated at 1,174/sq km. In all the rest, the density varies between 200 and 400.
- India has the maximum number of cases in the South Asia region.
- India, Pakistan and Bangladesh are almost the same in terms of total deaths per million population (20-25) and also same case fatality rate, which is around 2%. The total deaths per million population is 2 in Nepal; this may be because Nepal is yet to peak and spread is not yet seen.

- The situation in Sri Lanka is; however, different, despite similar population density. The case fatality rate is low (1%) as is the total number of cases.
- Analysis of the indicators of health infrastructure shows that all 5 countries have almost similar number of physicians per 1,000 people. But in terms of hospital beds per 1,000 population, Sri Lanka has the highest number (3.6); in India, Pakistan, Nepal and Bangladesh, this number if 0.5-0.8.
- Sri Lanka and India reported their first case of COVID-19 at nearly the same time; 27th January and 30th January, respectively.
- All 5 countries implemented lockdown around the same time, but Sri Lanka extended the lockdown much longer.
- More than 10% positive rate practically means community transmission and if less than 5%, then lockdown can be lifted. India, Pakistan and Bangladesh have more than 10% positivity rate.
- Reasons for low mortality in Sri Lanka: First in the region to eliminate malaria, better hygiene index, educated population, better infrastructure, extended lockdown.
- Kerala has similar mortality as that of Sri Lanka (0.3%); total cases are 23,000 cases and only 74 deaths. The seroprevalence is less than 10%. The seroprevalence in Delhi and Mumbai and Pakistan is around 20-30%. In Bangalore, seroprevalence is 10-12%.

COVID-19 in China, South Korea and Singapore

Dr Yeh Woei Chong

- **China:** Confirmed cases 84,292 (discharged 78,974, deaths 4,634); cases have been rising from last 1 week. From 11th June to 23rd June, there were 256 cases in Beijing. Prior to this, there were no cases for 55 days. The trigger is a seafood market like in Wuhan and the source of infection apparently is contaminated chopping boards. China has a huge testing capacity; it is testing people in large numbers – half million tests daily. Outbreaks in Dalian and Xinjiang in the last week; the new outbreak in Dalian has been linked to a seafood company and contamination from packaging is suspected. On 30th July, there were 11 cases in Dalian and 112 in Xinjiang.
- **South Korea:** There are more than 14,000 confirmed cases; 13,183 have been discharged and around 300 have died due to the infection. There is a second wave in South Korea. The number of cases is increasing. There were 113 cases on 30th July. South Korea has done 1,563,796 tests. Their clusters are nightclubs, door-to-door sales, churches, ports and nursing homes.
- **Singapore:** There are around 52,000 cases. Majority of cases in the country are in dormitories housing migrant workers (around 50,000), while the community has only around 2,000 cases. Last week, there were 400 cases in dormitories and 5 in the community. Around 5,400 cases are in isolation. Since February, there are 128 ICU cases; this number has been zero since last 2 weeks. Number of tests performed is 1.23 million. There are 323,000 migrant workers in dormitories. Of these, 262,000 have recovered or cleared of the virus. Efforts are on to clear all the dormitories of COVID-19 by 7th August. Migrant workers are swabbed every month towards this end. 975 factory dorms + 64 blocks in 17 purpose-built dorms have been cleared. Everybody is swabbed and if there are any cases, swabbed again after a week; 13,000 swab tests are done in a day.

Hong Kong Update

Dr Alvin Yee-Shing Chan

- Hong Kong is experiencing the third wave (July) with 3,271 cases and 27 deaths, which is serious; up to end of June, there were 1,200 cases and 8 deaths; in second wave in April, the maximum number was only 65.
- Origin of the third wave is from sea men and air crew who were exempted from quarantine and routine testing together with relaxation of rules of social gathering and fatigue set in.
- No capacity for *en masse* testing; bottleneck of testing 13,000 daily; now screening started for high risk groups – people working in restaurants, catering, sellers, etc. No exemption now from testing and quarantine.
- Manpower is adequate; 6,219 doctors in public hospitals; only half of public hospital beds are occupied in the past 2 months as all elective surgeries have been postponed in public hospitals.
- T614 gene mutation was found in cluster of sailors entering Hong Kong from Kazakhstan and Philippines; this DNA expression is similar to that seen in many people in Hong Kong infected in the third wave. Patients became more serious and more infectious.
- Virology Department in the University of Hong Kong is working on research to produce a vaccine against COVID-19.

- Holiday homes/villages/resorts have been modified as isolation and quarantine centers for mild cases to prevent cross infection to family members.

The Risk of COVID-19 Transmission in Train Passengers: An Epidemiological and Modelling Study

Despite the trains being one of the commonest modes of public transport across the world, the risk of COVID-19 transmission among individuals traveling by train remains ambiguous.

The study was conducted retrospectively to quantify the risk of spread of COVID-19 on high-speed train passengers. The data was collected from 2,334 index patients and 72,093 close contacts who traveled together for 0-8 hours from 19th December, 2019 through 6th March, 2020 in China. The researchers analyzed the spatial and temporal distribution of COVID-19 transmission among train passengers to assess the link between infection, spatial distance and co-travel time.

The study findings showed that the attack rate in train travelers on seats within a distance of 3 rows and 5 columns of the index patient varied from 0% to 10.3% with a mean of 0.325, while patients sitting in the same row seat as the index patient had an average attack rate of 1.5%. This was higher than those in other rows, with a relative risk of 11.2. The study clearly showed that patients sitting adjacent to the index patients were at the highest risk. The attack rate reduced directly in proportion with the increasing distance between the seats, but it increased with the increase in co-travel time.

The findings led to the conclusion that COVID-19 has a high infection rate among train passengers, but the risk significantly varies with co-travel time and location of the seat. Based on the study findings, the authors have recommended that during disease outbreaks, when traveling *via* public transport in restricted enclosures such as trains, adequate measures are necessary to lower the risk of spread of disease. These measures include increasing seat distance, reduced passenger density, and use of personal hygiene as protection.

Hu M, Lin H, Wang J, et al. Clin Infect Dis. 2020;ciaa1057.

Round Table Expert Zoom Meeting on "Consent in COVID Era – Need for Change"

1st August, 2020 (11 am-12 pm)

Participants: Dr KK Aggarwal, Dr AK Agarwal, Prof Mahesh Verma, Dr Ashok Gupta, Dr Shashank Joshi, Dr JA Jayalal, Dr Jayakrishnan Alapet, Dr Anil Kumar, Mrs Upasana Arora, Dr KK Kalra, Ms Ira Gupta, Dr Sanchita Sharma

Key Points from the Discussion

- COVID-19 has changed the scenario today. There is an inherent risk due to the changing nature of the virus.
- The requirements of presurgical patients are different; patients require more ICU stay.
- Institutes and hospitals must come out with new consent formats.
- Introducing the subject, Dr Kalra shared different modified formats of consent from the American Society of Plastic Surgeons and the Indian Journal of Surgery.
- Time has come to revisit consent. Consent should now be "fully" informed consent and not just informed consent and also include informed refusal.
- Blanket immunity may not work.
- There is now a need to shift from written informed consent to video, record consent in audio-visual format.
- There should be transparency in information provided to the patient. Include probable points so there will be no counterpoints. Make it "foolproof".
- The regular consent form in a pre-printed format is outdated. In a recent order in July, the National Consumer Disputes Redressal Commission (NCDRC) has held that the use of pre-printed consents forms is not valid.
- Consent should be in the patient's language, which he/she can understand. Consent will change in every counseling session.
- MCI Code of Ethics regulations specify that consent should be given by the patient or the spouse. In the COVID era, both husband and wife may be infected and may be hospitalized. So, now the "next of kin" should be identified for consent. Also, identify someone who will pay (guarantor).
- For a patient under isolation, the routinely taken consent may not be valid; it can be challenged on the grounds that the patient was under mental stress, etc.
- Shift from consent to agreement; now a detailed consent will be required, and every step should be recorded.
- The landmark Samira Kohli judgment took into consideration the Bolam's rule under which complications that occur <1% need not be informed to the patient/family. But now the definition of consent will change from this.

- Include the words "as on today" in the consent when giving information to the patient as new information about COVID is emerging almost every day.
- We need to define guidelines; they are not mandatory; treatment may change from the guidelines based on the professional competence of the treating doctor. This needs to be included in the consent. Guidelines inflict on professional autonomy.
- Define "off-label"; every treatment in COVID is off-label use.
- Declare death when brain death occurs; do not wait for the heart to stop – follow organ transplantation guidelines for this. Extended cardiopulmonary resuscitation (CPR) not allowed. Define the hours or how long will the body be kept in the hospital. Include such information in the consent.
- Include a clause for do-not-resuscitate (DNR).
- Put in a clause for compensation; write down your in-house redressal mechanism in case of a dispute.
- Include clause of good faith.
- Clearly define isolation rooms in the consent; in the western literature, isolation rooms mean negative pressure rooms.
- Define presymptomatic cases in consent as sometimes patient brought in is negative for COVID-19 but may become positive during hospitalization. This may become a dispute.
- Be transparent about charges (ethical); whether insurance will cover or not.

Re-testing Positive

RT-PCR can be Redetected But not Re-positive

- A positive real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) antigen test is highly accurate, pointing to the presence of SARS-CoV-2 RNA.
- There seems to be no significant cross-reactivity with other respiratory viruses or other coronaviruses.
- A study from Korea suggests that patients with persistent positive tests, beyond 10 days from the initial positive test, who do not have any symptoms are no longer infectious.
- For patients with a high suspicion of COVID-19, a negative test should not exclude the infection.
- The number of false-negative results is not clearly known, though the resultant risk is high.
- Several factors affect the odds of a false-negative test, such as the time when the sample was collected in relation to the timing of illness and the type of specimen collected.
- Nasopharyngeal swabs are likely more accurate compared to nasal or throat specimens.
- Repeat or serial testing enhances the sensitivity; however, it may not always be available.
- rRT-PCR is the current standard, yet, more inclusive consensus-based criteria would possibly be introduced due to the concern about false-negative results.
- Patients who are discharged from isolation after recovery and who again test positive for SARS-CoV-2 are not likely to be infective, suggests a report from the Korea Centers for Disease Control and Prevention (KCDC).
- There's no relapse.
- The disease is known to linger and to affect more than one system of the body. But, other viral diseases, such as influenza and mononucleosis, also work the same way.
- As of May 15, researchers in Korea had identified 447 patients who tested positive again on RT-PCR testing for viral RNA. Of these, 63.8% patients had undergone epidemiologic investigation and contact investigation. Of those tested, 59.6% were tested for screening purposes and 37.5% were tested as they had symptoms. About 44.7% of the 284 patients who underwent investigation were symptomatic.
- Data obtained from three groups of patients from different cities revealed that 25.9-48.9% of the patients again tested positive after discharge.
- Among the 226 symptomatic patients, when their case was initially confirmed, a repeat positive test result after discharge was noted an average of 44.9 days from the date of initial symptom onset. The average duration from the time of discharge to the time of the second positive test was 14.3 days.
- Nearly 60% of patients who tested positive a second time underwent a test for screening purposes, irrespective symptoms. Of those who again tested positive, 44.7% had symptoms such as cough and sore throat.
- In order to ascertain if a positive result on a second test was associated with infectivity, researchers assessed 790 contacts of the 285 patients who tested positive a second time. Of these, 351 were family members and 439 were others. Among the

contacts, 3 new cases were detected. But for these 3 patients, other sources of infection were possible, including religious groups or family groups in which there were persons who were confirmed to have COVID-19.

- The researchers tried to culture virus from 108 patients who tested positive a second time; all such cultures were negative.
- First and second serum samples were obtained from 23 patients who had tested positive a second time. About 96% of these tested positive for neutralizing antibodies.
- Active monitoring, epidemiological investigation, and laboratory testing of re-positive cases and their contacts showed no evidence to indicate infectivity of re-positive cases.
- Patients who have been discharged from isolation do not require further testing and are not likely to be infective, despite again testing positive on RT-PCR assay.
- The patients will no longer be considered as 're-positive cases' but as 'PCR re-detected after discharge from isolation'.

Medscape excerpts

RT-PCR Memory T Cells

A spurt of new studies has shown that a large proportion of the population — at some places, around 20-50% of people — might carry T cells that identify the new coronavirus despite having never encountered it before. Although it's too early to ascertain how helpful they might be, but even a slight influence on immune response could make the disease milder.

While the new coronavirus was unknown until 8 months back, yet to some human immune cells, it was already something familiar.

This could be a case of family resemblance. For the immune system, pathogens with common roots can look alike, such that when a similar pathogen comes to call, the body may already have a clue of its intentions.

The presence of T cells has fascinated the experts, who state that it is too early to be able to tell if the cells will play a helpful, harmful or negligible role against the new coronavirus.

However, if these T cells exert even a modest influence on the body's immune response, the disease might become milder. This could, in part, explain why some people become very sick while others don't. (*New York Times Excerpt*)

SARS-CoV-2-specific T-cell immunity in COVID-19, SARS and uninfected controls

Memory T cells that are induced by previous pathogens can build the susceptibility to, and clinical severity of, subsequent infections. There is limited information about the presence of pre-existing memory T cells in humans with the potential to recognize SARS-CoV-2.

In a recent paper published in *Nature*, researchers assessed T-cell responses to structural (nucleocapsid protein, NP) and nonstructural (NSP-7 and NSP13 of ORF1) regions of SARS-CoV-2 in 36 COVID-19 convalescents. Investigators noted the presence of CD4 and CD8 T cells recognizing multiple regions of the NP protein in all of them. Twenty-three SARS-recovered patients were still found possess long-lasting memory T cells that were reactive to SARS-NP nearly 17 years after the 2003 outbreak, showing strong cross-reactivity to SARS-CoV-2 NP.

SARS-CoV-2 specific T cells were also identified in individuals with no history of SARS, COVID-19 or contact with SARS/COVID-19 patients (n = 37).

SARS-CoV-2 T cells detected in uninfected donors had a different pattern of immunodominance, frequently targeting the ORF-1-coded proteins NSP7 and 13 as well as the NP structural protein.

Epitope characterization of NSP7-specific T cells exhibited recognition of protein fragments with low homology to 'common cold' human coronaviruses, but it was conserved amongst animal beta-coronaviruses.

Therefore, infection with beta-coronaviruses tends to induce multi-specific and long-lasting T-cell immunity to the structural protein NP.

Understanding how pre-existing NP- and ORF-1-specific T cells present in the general population affect the vulnerability and pathogenesis of SARS-CoV-2 infection is important for the management of the COVID-19 pandemic.

Le Bert N, Tan AT, Kunasegaran K, et al. Nature. 2020;584(7821):457-62.

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