COVID-19 – Experiences, Experiments, and Ethics:
A Webinar Report

A webinar was convened by Dr. Ashwinikumar Raut, Hon. Director Clinical Research and chaired by Dr. Rama Vaidya, Hon. Director Endocrine and Metabolic Disorders, Medical Research Centre-Kasturba Health Society (MRC-KHS), Mumbai on 23rd July 2020.

Since December 2019, COVID-19 has spread globally, literally bringing the world to a halt. India too has suffered the brunt of this devastating medical emergency. This webinar conducted by MRC-KHS captures various aspects of the disease. Trans-system physicians and multidisciplinary biomedical scientists participated. India has a pluralistic system of medicine, and it was essential to discuss multi-system inputs. However, it was heartening to find that physicians from various systems, when deputed to COVID-19 centres, had uniformly followed the Government of India guidelines for the diagnosis and management of COVID-19.

Welcoming the delegates at the webinar **Dr. Deepak Dave, MD, DGO, the Hon. Medical Director** said that the greatest problem faced by the medical profession today is that there is no effective treatment yet available for COVID-19. The spread is silent and the pandemic has medical, social and economic impacts on people.

Dr. Tanu Singhal, Consultant, Pediatrics and Infectious Disease, presented current standard management of COVID-19 and shared her personal experience and practices followed at Kokilaben Ambani Hospital, Mumbai.

Dr. Singhal alerted that early diagnosis is the key to effective management. She said that symptoms of COVID-19 are common knowledge now and RT-PCR test is the gold standard. Care must be taken during collection and transportation of nasopharyngeal swab, she emphasized. It should be collected early during the disease. Moreover, under the best of circumstances the test may be negative in 30% cases, hence negative doesn't rule out COVID-19. Nevertheless CT-chest complements the COVID-19 diagnosis. Dr. Singhal clarified that antibody tests are not for diagnosis of acute infection nor are they immunity passports for future protection.

Mild COVID-19, Home-Isolation and COVID-19 Management

In mild COVID-19, a person may have some symptoms like fever, myalgia, headache etc. with no respiratory distress and the room air saturation after exercise remains >95%. In mild COVID assess the age, co-morbidity and isolation facility at home with a separate toilet. Young patients without risk factors and facility at home for isolation can be treated at home. Elderly persons also with co-morbidities and without sickness and who have facilities at home with people to look after; can be treated at home with prompt access to medical care.

The treatment for people under home isolation is paracetamol with proper monitoring of their fever, adequate intake of fluids and nutrition. Empirically, Zinc and Vitamin C are also given. Role of Hydroxychloroquine (HCQ) and Favipiravir is paradoxical. Steroids should not be given in early mild cases. The three red flags are breathlessness, if fever persists beyond 7 days or oxygen saturation < 95% at rest or after 5-minute walk.

Moderate to severe disease is when a person has dyspnoea or breathlessness and tachypnoea (RR >24/min) and if SpO2<95%. People with saturation at room air 90-94% should be treated appropriately as otherwise they could worsen quickly. The drugs for management of moderate to severe COVID-19 are: Glucocorticoids; dexamethasone/ methylprednisolone for a period of 5-10 days as early as possible on admission. Remdesivir has now been approved and is used for moderate to severe COVID-19 infections. Tocilizumab is used in hypoxic patients with high IL-

6. Recently, they have started using convalescent plasma. Antibiotics are not routinely given.

Dr. Singhal stressed that treatment did not end with recovery as many of the patients need to be watched after discharge. They need to be given oral anti-coagulants, if indicated. They are advised to monitor their oxygen levels using pulse oximeter. Pulmonary function tests need to be carried out after 2-3 months as many patients develop irreversible lung fibrosis.

Dr. Singhal also enumerated some of the grey areas in the management of COVID-19:

- A 65-year old patient with IHD and respiratory disease and now has mild COVID. Would it be right to give Remdesivir straight away to prevent further disease severity?
- What about people who have fever for more than 7-10 days with no hypoxia? Can Remdesivir and steroids be given?
- What about people with mild disease or persistent fever with CT evidence of lung involvement? Can Remdesivir be given?

Dr. Geetha Balsarkar, Professor, Wadia Maternity Hospital, Mumbai, show-cased the problems of COVID-19 and pregnancy. About 85% patients had mild disease, 10% severe disease and 5% critical disease. Comorbidities, such as obesity, diabetes, asthma, hypertension may make pregnant women more susceptible to the effects of COVID-19.

If a patient comes with COVID-like symptoms, alternative or comorbid processes are needed. Laboratory derangements may overlap with other obstetric diagnoses e.g. transaminitis and pulmonary findings can confound a diagnosis of preeclampsia or HELLP syndrome. If patient develops new signs/symptoms during hospitalization or labour, COVID-19 needs to be considered regardless of a priori-risk of other infectious processes. Patients may present early in their infectious course prior to symptoms, or may have asymptomatic viral carriage. Less than 5% asymptomatic women tested on labour and delivery were positive for SARS-CoV-2.

COVID-19/SARS-CoV-2 appeared to have less severe adverse pregnancy outcomes than MERS/SARS-CoV-1. Complications of respiratory viral illnesses included preterm labour, premature rupture of membranes, intrauterine growth restriction, intrauterine fetal demise, neonatal death. Evidence of SARS-CoV-2 crossing the placenta and infecting the fetus is lacking; however, few cases of possible in-utero infection have been reported.

In case of ante-natal patients with COVID-19 symptoms; labour is allowed to progress with monitoring with minimum interventions and avoiding general anaesthesia. Vaginal delivery is not contraindicated. Data on prenatal transmission did not preclude the use of forceps/vacuum. An operative vaginal delivery may be considered to shorten the second stage since active pushing with mask-on may be difficult for the patient. Caesarean delivery should be performed in operating room with negative pressure. Placental tissue, miscarried embryos/fetuses is treated as infectious tissues and disposed-off appropriately.

Remdesivir is an investigational agent and pregnancy is exclusion for participation in trials. However, it is available for pregnant-women with severe COVID-19 manifestations. Immunomodulators like anti-IL6 agents can also be used. Since, Tocilizumab crosses the placenta it may only be considered for use in pregnant-women who have severe or critical COVID-19 and suspicion of cytokine-activation syndrome with elevated IL-6. HCQ also crosses the placenta but is considered safe to use in pregnancy and also in lactating mothers.

Dr. Ashwinikumar Raut lamented that no specific medicine for COVID-19 was so far available. Hence there was an urgent need to investigate through research an evidence-based product which would help overcome novel SARS CoV-2 and control the disease COVID-19. There was ample scope to investigate Ayurveda-herbal products in this context, he said

MRC-KHS Research Director, Dr. Ashok Vaidya took an early initiative to sensitize the Ayurveda stakeholders in government and industry. He sent an email shortlisting four plants which have potential to develop as useful products for COVID-19 if developed on a fast track following reverse pharmacology path. This approach was further illustrated in the article published in the May 2020 issue of *The Indian Practitioner*.

Prof. Bhushan Patwardhan, Vice-Chairman, University Grants Commission, New Delhi. Took immediate action and an interdisciplinary AYUSH-task force for research and development related to SARS CoV-2 and COVID-19 was formed. MRC-KHS's Director Clinical Research Dr. Ashwinikumar Raut was invited to join this task force in the working group to plan and execute clinical trials for pre- and post-infection prophylaxis of COVID-19. This notification came in the first week of April 2020. The task force had

seven such working groups with an ambitious plan.

After sufficient debate and discussion amongst experts, two platforms of clinical investigations were planned viz. Prophylaxis with an *Ashwagandha* in comparison of Hydroxychloroquine in health care providers, and Add-on Ayurvedic formulation alongwith a standard care management in patients of COVID-19. For this add-on therapy, three products viz. AYUSH-64, *Guduchi-pippali* and *Yashtimadhu* were finalized. AYUSH-64 as an add-on remained with AYUSH whereas, other three products were taken up by CSIR.

So far AYUSH-64 study patient enrollment has been completed and other three projects would start soon.

Dr. Madhura Kulkarni, MD (Ayu-Gynaec & Obs), Diploma in Yoga & Philosophy, shared her experience of working in a municipal clinic at Thane. The team consisted of two medical officers & 35 health workers who maintained positive health profile during this pandemic. They conducted surveys as well as camps in localities & positive health awareness regarding COVID-19.

A holistic protocol 'Protecting the Protectors' was devised for the health workers. This comprised of early morning consumption of *avla (Phyllunthus embilica)* and *haldi (Carcuma longa)*, before lunch *shunthi* (Ginger), during lunch *meeri* (black pepper) and after lunch *ajwain* (Carom seeds). They also did breathing exercises, *pranayams*, meditation, oil-based *nasyas* (nasal instillations), steam inhalation and gargles. From mid-March till July not a single case of COVID-19 was reported amongst this group. *Ayush kadha* was also consumed at the center by all. This model used is useful as a prophylaxis.

Dr. Kulkarni also developed a holistic model to treat COVID-19 patients with *Satva-parikshan*, *Prakruti-parikshan* and *Agni-parikshan*.

Dr. Surabhi Khemka, Consultant Homeopath, MRC-KHS recounted her experience from the opportunity she got to work at a COVID centre, NESCO, Mumbai. It was a Centre for mild to moderate cases and had a capacity for 1000 patients. It was a much organised centre with a separate building called the 'control room' which would take care of all the requirements.

The other amazing feature was a software which could be accessed from the ward/the booth/the control-room. So, each and every patient was tracked by doctors in the control-room. Separate person in-charge to upload the patient data helped access to latest update on any patient.

What was most impressive was that all the deputed doctors, whether belonging to conventional medicine or any of the AYUSH trans-systems had to follow the diagnostic and treatment guidelines laid down by the Government. So Dr. Khemka also had to treat patients at the NESCO centre – not through homeopathy –but by the diagnostic and treatment guidelines laid down by the government.

This was a great learning experience that helped develop her clinical judgement for COVID-19, understanding the biomarkers, and picking-up cases at potential risk of cytokine storm. Trans-disciplinary doctors gained greatly through medical knowledge exchange opportunity with doctors from other disciplines.

She also treated a mother and daughter who refused to be tested for COVID due to fear of being quarantined outside their home, though they had all the clinical symptoms of COVID. On the 7th day as the treatment continued, while the rest of the family tested positive, the mother – daughter duo tested negative. However, after another week their IgG antibody for COVID-19 came positive indicating that they had also contracted COVID-19. So, wasn't the fact that the mother-daughter duo tested negative due to homeopathic treatment, she wondered? However, she said she was not claiming this, as it needs further investigation. A detailed write up on Homepathy and COVID-19 by Dr. Khemka is also published in this issue of *The Indian Practitioner*.

Dr. Shobha Iyer, Research Associate, MRC-KHS recalled how at end of June 2020 her father-in-law, herself and her husband developed fever in turn. Though her husband and she recovered with the medicines prescribed by the local physician (Paracetamol 650mg and Azithromycin 500mg), her father-in-law continued to have temperature around 100^{o}C with CRP 65mg and SpO2<93%. Meanwhile, she slowly realised that she was unable to smell anything including the strongest perfumes. Moreover, both her father-in-law and husband had certain co-morbidities which also created a sense of tension at home. But to their surprise her husband and herself tested positive and her father-in-law tested negative for RT-PCR. The government medical officer suggested home quarantine for both of them since they had mild symptoms. Meanwhile, though her father-in-law tested negative, his oxy-

gen level had dropped down to 82% and hence was immediately shifted to hospital where he was diagnosed with pneumonia and later COVID-19 positive. During home quarantine, they were prescribed hydroxychloroquine 400mg twice a day for the first day and 200mg twice a day for 5 days, azithromycin 500mg once for 5 days, Zinc-multivitamin-multi-mineral tablets, calcium-vitamin-D and vitamin-C. They were visited by the Medical officer every two days and were also monitored over telephone daily. While they were on HCQ, they had nausea and early morning bile-acid reflux. During the course of medicines, her husband became very weak since he had diarrhoea, loss of appetite and fatigue. When they reported this to the Medical Officer, it was attributed to the side-effect of HCQ which would subside after the course was completed. However, oral-rehydration-therapy helped a lot. Apart from the medicines, they did steam inhalation and breathing exercises 5-6 times a day and consumed 'Kadha' suggested by AYUSH. She started regaining her sense of smell. After they completed the course of medicines they started feeling better with good improvement in appetite and became more active. After 14 days of quarantine, they both tested negative. Other elder family members also tested negative for COVID-19 despite having certain co-morbidities. It clearly shows that the virus cannot affect people with strong immune system and positive mind. Her father-in-law also was discharged from hospital after 12 days with gradual improvement in his health.

Dr. Jayashree Joshi, Jt. Research Director KHS-MRC, said that the National ICMR COVID-19 related guidelines released in April 2020 were followed by all. ISBEC (Inter System Biomedica Ethics Committee) received requests for evaluation of 10 project protocols; 4 were resubmitted and had been approved. The Chairman had been frequently consulted by the Drug Controller General of India (DCGI) and other national bodies for various new projects, regulations for clinical trials, and DCGI guidelines. All EC members were active in independent capacities also during this period. Some published original research papers and most attended webinars related to Center for Development studies and Activities (CDSA), COVID-19 and other professional meetings. One member was active in the national COVID-19 AYUSH Task-Force meetings and resultant clinical trials.

New Classification:

i) Ongoing Clinical Research-modifications for COVID-19 pandemic
ii) New Non-COVID-19 research iii) COVID-19 related research and relevant guidelines are to be followed by all.

Due to COVID-19-related restrictions for patients, volunteers, health-care workers, investigators and EC members, use of internet and electronic systems was recommended.

Dr. Kiran Marthak, MD, FCCP, Clinical Research-Scientist elaborated how the COVID-19 pandemic had created havoc all over the world.

Due to lock-down situation, clinical trials worldwide are affected. To circumvent this situations Regulatory Authorities of the world e.g. US-FDA, EMEA, MHRA, ANVISA, TGA and ICMR have published the guidelines for the conduct of clinical trials for the safety and well-being of the trial participants such as;

1) Sponsor can decide to continue the clinical trial or temporarily discontinue the clinical trial or completely stop the clinical trial depending upon the risk benefit ratio.
2) There could be protocol amendments which needs to be in consultation with the Investigators, Ethics Committee and the Regulatory Authority.
3) In emergency, Investigators can modify the protocol or the process even without informing Ethics Committee and the Regulatory authority as well as the sponsors.
4) Patients can be monitored by telephone or by video calls and the records maintained for the same.
5) Patients can carry out investigations near their home which can then be entered in the Case-Record-Form.
6) The trial material can be sent to the patients by courier service with the clear instructions about mode of administration.
7) Ethics committee can meet over the telephone or on video conferencing maintaining all the digital records.
8) The inspection/auditing by the inspectors from the Health authority can be carried out over Digital technology.
9) If the clinical trial is for COVID-19 patients itself and the patients are isolated the informed consent of the patient could be obtained over the mobile telephone in front of the witness and the record should be maintained accordingly.

Dr. Raut's Conclusions:

Dr. Raut highlighted the key points of each presentation in his final observations. He emphasized that the answers to the relevant queries raised by Dr. Singhal would only come as we get more informed by clinical experience. We need to formulate appropriate research questions and execute properly planned research experiments, he stated.

Dr. Raut said that while the research program he was involved with is ongoing, the experience and difficulties in conducting the clinical trials were unique, right from obtaining the patient consent, indoor management, day to day data entries in CRFs and discharging patients in view of ever changing/evolving new norms. The study intervention they have undertaken would continue till three months. This gives the scope of observing these patients in their post-recovery phase and also monitor the re-infection possibility with or without interventional drug. The distinct feature of this project is that it undertakes extensive laboratory investigations and also records Ayurvedic evaluations. In a true sense they have adopted an integrative approach.

He appreciated Dr. Kulkarni's excellent observational prophylaxis study for COVID-19. This needs to be properly documented and subsequently published.

Dr. Raut said that Dr. Khemka's experience in homeopathic treating of a mother and child and her meticulously made observations need further reporting as a case study with potential effectiveness of Homeopathy in COVID-19.

He particularly highlighted from Dr. Khemka's experience at NESCO, how the COVID crisis has brought together doctors from different systems of medicine due to the emergency requirement of medical personnel. He said that such inter-system interactions and its dynamics immensely help in enriching medical practice for the holistic healthcare of human beings.

Finally, he thanked all the speakers for sharing their valuable experiences, Dr. Rama Vaidya for accepting to chair the session, Dr. Deepak Dave for giving the opening remarks and all the participants for their active participation and patient hearing. Dr. Raut concluded that if we truly take the lesson from this pandemic, we would evolve as more creative, progressive and cooperative human society.

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