The Suno India Show

The need for evidence-based medicine in treating COVID-19

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Sandhya Srinivasan: *A number of old drugs that have been approved for other diseases are being "repurposed" and tested for their safety and efficacy in COVID-19, in systematic clinical trials. They have emergency approval for use in COVID-19, but most are not yet proven for this use. Some drugs have received approval without adequate testing. Other drugs are being used without getting approval for use in COVID-19. Now, all these drugs are being prescribed widely by doctors, outside of clinical trials.*

In this episode, I spoke to Dr Shriprakash Kalantri, Director and Professor of medicine at the Mahatma Gandhi Institute of Medical Sciences, Sewagram, and medical superintendent of the Kasturba Hospital there. Dr Kalantri, who has been with MGIMS since 1981, heads an internal medicine unit, teaches medical students and also conducts research in collaboration with researchers from the University of California Berkeley in the US and McGill University, Canada. One focus of his work has been the epidemiology of chronic diseases at the primary and secondary levels.

Hi. I am Sandhya Srinivasan, consulting editor for the Indian Journal of Medical Ethics, and you are listening to The Suno India Show. This episode is part of our special COVID science series where we bring to you conversations with leading virologists, doctors, scientists and other experts on all things vaccines, drugs, ethics surrounding the research and development and access to these drugs and vaccines.

Dr Kalantri is a professional who is deeply committed to the use of rational medicine. He has always been speaking out against the unscientific practices that he sees around him. In the past few weeks, he's been very active on Twitter, as well as in the mainstream media, criticizing the use of untested medicines in COVID-19. Only a minority of patients of COVID-19 need medical care. This care is largely supportive, as there's no specific treatment and patients & their relatives are just desperate for a cure, and doctors feel under pressure to do something. And in this context, the beneficiaries are obviously the pharmaceutical companies which can encourage irrational prescribing practices.

Dr Kalantri, given that medical decisions must be based on evidence. Could you explain the different types of evidence that are used towards deciding whether or not a drug is effective?

Dr SP Kalantri: When we talk in terms of evidence, the best and the most popular evidence that we see in general practice is the doctors using their own experience. It's not uncommon to see doctors saying that "well in my last 40 years of experience, I have treated patients like this, and in my experience this treatment has really worked". But, in the entire hierarchy

of evidence based medicine, the so-called “experiential medicine” is ranked the lowest. What is more important is to base your clinical practice, your diagnosis, and treatments on the basis of layers of evidence. The evidence based medicine has got several steps. The highest step is called a Randomized Controlled Trial. By Randomized Control Trial, we mean that the people are randomized into two groups. Each group has an equal opportunity of getting a new drug or the current standard of treatment. These patients are then followed up. Then, the investigators count how many survived, how many died, how many benefited, how many did not benefit, how many had a side effect and how many escaped side effects. And then they say that “all things considered, treatment A is better than treatment B”. In the hierarchy of evidence based medicine, Randomized Control Trials are accorded the highest rank. Below that, we have Case Control Studies, Retrospective Studies, in which the doctors would be looking at the patient's charts and figuring out what worked and what did not work, or they would have a case series of probably 100-200 patients and would look at the data to figure out that probably, this intervention benefited and this did not. Most doctors are expected to follow the highest standards of evidence based medicine. So, the treatments they choose or the therapies they design to treat their patients should be based on Randomized Controlled Trials.

Sandhya Srinivasan: *What you are saying is that there are various study designs in research which give you different types of evidence. But, the Randomized Control Trial gives you the best type of evidence. The problem is conducting an RCT takes time. You don't have that kind of time to do an RCT when you're in the middle of an emergency. Is it reasonable in this situation to consider using these other kinds of evidence?*

Dr SP Kalantri: I agree with you that in a desperate situation where the condition of the patient is extremely critical, there are no guidelines, there are no RCTs or it is difficult to conduct an RCT, then we need to go to the next step of the hierarchy. Probably, the observational trials are completely justified. I would argue that even clinical experience of the doctors or the conventional wisdom must be used because saving the life of a patient or making sure that the patients are benefited is at stake. This particularly occurred in the Ebola epidemic in 2014, when the mortality due to Ebola was extremely high in some of the poorest countries in the world. It was nearly impossible to conduct Randomized Control Trials. The resources were extremely limited, it was nearly impossible to plan, execute and design a control trial. At that time, even the World Health Organization permitted, and said that given these situations, we would make an exception and even the treatments based on your own observations or case series or observational controlled trials would be perfect, but you must remember that there are exceptions and these exceptions must be used in exceptional and desperate conditions only, and they should not be used as a truth.

Sandhya Srinivasan: *Some important interventions that have been advised in COVID-19 are not based on evidence from an RCT to make a decision. One example is the use of masks.*

There is no RCT on masks, but no one has questioned the advice on the universal use of masks.

Dr SP Kalantri: Great question. I agree with you Sandhya. There is no evidence on the basis of Randomized Control Trials which either refute or confirm the use of masks in preventing, or at least, reducing the viral transmission in the communities. Just a month back, Lancet, one of the most prestigious journals in the world, published a systematic review. The systematic review looked at about 25,000 individuals wearing the mask and comparing them with an almost equal number of individuals who are not mask wearers. It concluded that compared to people who do not wear a mask, mask wearers are expected to have an 85% reduction in the risk of acquiring a COVID-19 infection. This is a huge reduction. Now, given this evidence generated by systematic review, and given the fact that right now the entire world is seized with a pandemic, it would be extremely unwise or even I may say, unethical, to put an RCT on the use or no use of mask because logistically, today, nobody would agree not to wear a mask or to be put in the control arm. Right now, probably, we don't need an RCT, where we have clinical experiential wisdom. We have got good data from systematic reviews, which very clearly shows that wearing masks greatly reduces your chances of acquiring viral infection from coronavirus.

Sandhya Srinivasan: *Still, masks were imposed much before that information was available, much before they were proven to work. Another example is the use of blood thinners. There is no RCT that has confirmed the benefit of blood thinners in COVID-19 but they are advised, and used in a procedure different from their standard use.*

Dr SP Kalantri: As for blood thinners, I must admit that we use them in almost every hospitalised patient with COVID nowadays. There are two reasons behind that. One, as I say, is our own observations and the efficacy of blood thinners in several other non-COVID related disorders. For example, when men and women above the age of 70 or 80 break their leg, they develop a fracture in their thigh bone, and are taken to hospital. It's a universal policy to put these people on blood thinners because the chances that they might get a clot in their leg veins, that these clots might find their way into their lungs and might kill them are extremely high. There is good evidence that the patients who are more likely to harbor this thrombi or clots in the leg veins or elsewhere, are more likely to be benefited by blood thinners compared to no treatment. As for COVID, several autopsy studies on patients who died of COVID-19 infection in the US, UK and Europe have shown a very novel phenomena. They found that virtually every organ in the body i.e. brain, lung, heart, liver, kidney was studied with micro thrombi. These patients were dying because of this thrombi or abnormal clots generated in response to a COVID-19 infection. It probably was not a virus that was killing them, but it was these blood clots in very important organs in the body that were fatal. I agree that there is no RCT but there are at least three RCTs which are going halfway through right now. These RCTs are likely to be published in September or October. Till such time, we get evidence from the unpublished RCTs. It would be extremely prudent, based on these autopsy studies and on our usual observations, that blood thinners would greatly

benefit COVID-19 hospitalized patients, especially those who are seriously ill, and on mechanical ventilators. We could be saving a lot of lives by this very simple and relatively inexpensive intervention.

Sandhya Srinivasan: *So what you are saying is that one does not actually have to always depend on RCTs. One uses the evidence from RCTs when they become available. But very often, one's medical decisions are the basis of experience, logic, commonsense. And, wearing masks makes sense.*

Dr SP Kalantri: If we look at the definition of what is evidence based medicine, this concept came about 2.5 decades ago, and it's the brainchild of a British physician and epidemiologist David Sackett. His definition of evidence based medicine, which he gave in 1996 is still valid today. How does David's define evidence based medicine? He says that evidence based medicine consists of judicious, explicit and conscientious use of best evidence. The best evidence would come from well designed adequate numbers, Randomized Control Trials. So, you pick up evidence from these RCTs. But evidence alone is not enough. You also need to add your individual experience, your wisdom, your knowledge, your skills, your hospital setting, your resources to this evidence. Even your experience is not alone. You should bring the patient on board and consider the patient's values, concerns, and the way he or she looks at life. Once you have got this three overlapping circles of best evidence, your own experience, and the patient's values, expectations and the way they look at their life, now decide the best therapy. Often, an evidence generated only on the basis of RCT might not work because, for example, what has worked in the UK and US might not work in the primary health centers in our country, because our resources are very different. What if a patient has got an aggressive outlook towards life and wants to fight his or her life every day for a stage four metastatic lung cancer? It's also important to incorporate your own experienced judgment, wisdom, patient's values, and then design a therapy, which probably would be the best therapy considering an individual patient.

Sandhya Srinivasan: *An RCT must be conducted properly in order to produce evidence. How do you determine what a good Randomized Control Trial is, or whether the RCT that you are reading about has been done properly?*

Dr SP Kalantri: First step in defining a good Randomized Control Trial is to first figure out whether there is a very clear cut meaningful research question or not. If the research question lacks clarity, the answers given by that Randomized Control Trial would be confusing and chaotic. The research question has to be right. There are ways and means to frame a proper research question. When you design a Randomized Control Trial, then it is important to ask yourself how many patients you need. In other words, this is called a sample size. To estimate a sample size, you need to find out what exactly you want to achieve. To give a real life example, if you have patients with heart attacks, and normally you find that 20% of them die, then you expect that by using a novel drug or an

intervention, you want to bring down this date rate from say 20% to 10%. You feel that you'll be very happy if there is a 50% reduction in mortality because of the new drug. Ask yourself that if you want to see whether this 50% reduction in mortality could be achieved by a novel drug, how many patients would you need to enroll to make sure that you're not making any errors? You must remember, at every conclusion that we base on the basis of a Randomized Control Trial, there will be some inherent errors, and you'd want to minimize those errors as much as you can. So, a good Randomized Control Trial should have enough patients, this is also called power of the study, and it should have enough patients to answer the very questions that you had started your Randomized Control Trial for. The two very important parameters, which tell us whether the RCT is good or ugly are blinding. Everybody, the researcher, the patient and the assessor, they should be blind. In other words, we should not know who got what. The moment we know who got what, there are inherent biases in our own mind and these biases would completely distort accuracy or truthfulness of a Randomized Control Trial. There are ways and means of reducing this bias. You should enroll the patients into two arms, and who gets what should not depend on your own value judgment, it should be completely left to a flip of coin, or nowadays, to computer generate programs, with a result that every person that you invite for a Randomized Control Trial should have an equal opportunity of being assigned to either a new drug group or with a conventional standard of therapy or a placebo. It should not be left to the hands of investigators because it creates a huge selection bias. Once you have assembled the participants, randomised them into two groups, masked yourself, and are reasonably sure that nobody's knowing who is getting what, then you follow these individuals for a reasonable period of time, count every outcome event, and these outcome events must be very clinically meaningful. What is the most clinically meaningful event for an RCT? To answer this question, I often get myself into the shoes of a common man. If I get admitted in an ICU, what would be the highest priority on my wish list? Would I go home or would I die? Therefore, mortality becomes the hardest and most clinically meaningful endpoint. In the process, you also collect data on how long the house patient was in the hospital, was the drug able to shorten his hospital stay or not, if the patient's BP improves, his blood glucose improves, or blood pressure or his kidney functions, we look at his white cell counts, we see whether his haemoglobin have been improved, whether the chest X-ray clears itself or not. But we must remember that all these things collectively are called surrogate markers. All these markers, your blood chemistries, your chest X-rays, all these are pure numbers. They are called surrogate markers. The surrogate markers are not very, honestly clinically meaningful to an individual patient. They might be important to generate more evidence to the future patients. But what is extremely important for a patient is the hardest clinical endpoint that is, will I die or will I survive? Will I be incubated and put on a mechanical ventilator or would I be spared from mechanical ventilator? How long will I be put in a medical ICU? A good clinical trial looks at the hardest, clinically meaningful endpoints, computes them, and then says that, well, all things being equal, patients who got a new drug had probably a 50% reduction in mortality compared to the current standard of therapy or current placebo. That makes a great RCT. There are several guidelines which tell

us what a good RCT is. One of the guidelines which researchers all over the world use is called consort guidelines, which has 20 odd points in a checklist. When these RCTs are submitted to the journal editors, the journal editors usually go through this checklist to figure out whether this RCT has followed all rules in the game or has been deviated substantially from them. If there are significant deviations, then those RCTs are considered not good. The results generated from these RCTs are not trustworthy. And these RCTs are called invalid RCTs.

Sandhya Srinivasan: *There are a number of major well designed Randomized Control Trials being conducted around the world looking at various medications and procedures or practices for COVID-19. Could you tell us about this systematic research?*

Dr SP Kalantri: One of the best RCTs which was published barely about a fortnight ago comes from the UK called the recovery trial. This recovery trial asked a great question, i.e. among hospitalized patients infected with coronavirus and who have an entire spectrum of illness (mild, moderate or severe), would dexamethasone, a steroid, able to cut down mortality. It is a great trial that has about 5000 individuals enrolled from 170 UK hospitals which conclusively showed that dexamethasone cuts the mortality by about a third in ICU patients and by about a fifth in patients who require oxygen support. This was great news for the entire world, given that dexamethasone is very cheap and people have a rich experience of dexamethasone, it is easily available in the ICU, and in Indian rupees, it costs no more than Rs.100 to Rs. 200 rupees for an entire course of therapy. A great RCT would not only show the efficacy of a drug but also show us that the cost effective therapies are available. Another RCT that I'd mention is a Remdesivir RCT conducted by the National Institute of Health, United States, where they showed that remdesevir, an antiviral drug, when given to the patients infected with coronavirus, can reduce their recovery time from 15 days to 11 days, but did not significantly impact their mortality. It means that this drug is not capable of reducing their death rates, but, was at least, capable of reducing the length of stay in the hospital by about four days, which some people feel is a significant event. By contrast, the great negative trial comes from the solidarity trial, funded by the World Health Organization. It clearly told us that hydroxychloroquine, the drug which created a lot of hype and hope worldwide in the last three months, failed miserably when it was given to the hospitalized individuals. The trial was cut short halfway through because of ethical reasons and that there were no clear benefits by Hydroxychloroquine. There was no point in subjecting the trial participants to the serious side effects caused by hydroxychloroquine. These three great examples very clearly show that if we're able to gather good clinical evidence by good RCTs, dexamethasone is a clear example that a drug worked, Remdesivir is a clear example that the drug partially works and hydroxychloroquine is a great example that the drug did not work. As we get this data and start applying it to the care of our individual patients in the ICU, we will be saving more lives, cutting down more side effects and after many years, we will be able to inject evidence into our day to day decision making for highly lethal infectious disease.

Sandhya Srinivasan: *You have mentioned that the Remdesivir trial was well-designed. There was some criticism about the conduct of this trial. When the trial started, the primary outcome was whether remdesivir reduced mortality from COVID-19. Before the trial was completed, the primary outcome was changed to how long it took patients who survived the disease, to recover. This has been criticised.*

Dr SP Kalantri: Yeah, I agree with you that the beauty of this trial is the fact that this trial was completed just in 56 days, which is almost a record. You start enrolling your first patient into the clinical trial, and then you enroll about a thousand patients in the trial, complete the trial and then publish the trial very rapidly in New England Journal of Medicine. That is a great achievement. The reasons are best known to themselves. They're quite inexplicable to me. They change the goalposts. The initial primary outcome was mortality and then they changed the goalposts. We don't know why they did that. This occurs usually in pharma funded clinical trials, where they want the trials to look much better than what they really are. They want to market these drugs. And probably, when they are not very happy that they are not able to achieve a primary endpoint, they look at secondary endpoints or surrogate markers and use them to prove that the trial has really worked, and then start marketing. I'm not sure as to why exactly Antony Fauci and Clifford Lane did that. Maybe, we'll have to wait some time to figure out what exactly went on in their minds and what made them do that.

Sandhya Srinivasan: *There is a lot of hype about drugs such as Favipiravir. People are lining up outside pharmacies to buy these drugs and they're even being sold in the black market. What is the evidence supporting the use of this drug?*

Dr SP Kalantri: Favipiravir is an oral antiviral drug that was promoted by an Indian pharma company based on extremely thin evidence. What is the evidence generated by this pharma company to show that this works? It asked about 12 major hospitals in the country- half of them are corporate hospitals, half of them are teaching hospitals in the country. It asked them to assemble 120 patients; these 120 patients were randomized into two arms. One group received Favipiravir and the other group was receiving standard care of treatment. All these patients had mild illnesses. It means that most of them had only a small fever or cough or cold or headache or body pain. None of them had hypoxia, which means that none of them were seriously ill. Then they looked at what proportion of patients the virus clears itself, or in what proportion of patients the chest shadows improve. These were their endpoints. I have several objections for favipiravir. 12 major hospitals in the country could generate only 120 patients for a drug trial? They are extremely prestigious national institutes in the country. The sample size was very small. Secondly, you are using a drug for a mild respiratory illness in which almost 98% of patients are destined to get better of their own. Tomorrow, if I develop a cough or a runny nose, or a small fever, why should I spend about Rs. 12,500 from my pocket for 14 days therapy for a drug, which is totally untested

and is unlikely to help me beyond a certain decimal point. The problem with these newer drugs, whether it is favipiravir or tocilizumab or newer drug promoted by a pharma industry, caught the public, policymakers, politicians, almost everyone for all the wrong reasons, or even convalescent plasma is that, so much hype and excitement as been created around them, and tomorrow, if you want to test these drugs in a proper Randomized Control Trial, it would be extremely difficult to find people in the control group. Some of my friends who are working in the ICUs in Mumbai tell me that every Mumbaikar today knows about Remdesivir. So, if tomorrow, in India, we want to launch an RCT in say, Mumbai on Remdesivir or even Favipiravir, the RCT would fail miserably because nobody wants to get into the control group. Now everybody would say that we want to be in the active group. This is a great problem when we start celebrating and sharing these stories prematurely in the media, when we create a lot of hype around these drugs in the media and when people feel that these are completely tested and proven drugs, and that they're likely to save their lives, then people would completely lose their faith and belief in science.

Sandhya Srinivasan: *Convalescent plasma therapy is another very frequently prescribed therapy and we see frantic calls for plasma donors. The Maharashtra government has announced the setting up of the world's largest convalescent plasma therapy and trial centre in the world. What is the evidence in support of convalescent plasma in COVID-19?*

Dr SP Kalantri: Convalescent plasma was used in 2014, 2015 and 2016 in Ebola. Contrary to what most of the investigators probably hoped for, it failed miserably. As of now, convalescent plasma has the same status that it is an unproven and untested drug, which means that we don't know whether it would benefit or harm. The best way to assess the efficacy and safety of convalescent plasma would be to test this drug in a proper Randomized Control Trial. But when our own politicians and Chief Ministers start taking pride that we have established the largest plasma bank in the entire world, when we start quoting anecdotes that a certain politician was administered plasma and he recovered within 24 hours of plasma, people start pursuing plasma as a magic bullet. Going back to mythology, it's a Sanjivin booti for comatose Lakshman and the convalescent plasma would probably bring people from the tightening jaws of death. In Maharashtra we just started a Randomized Control Trial on plasma. My colleagues keep telling me that when they try to randomize people into the randomized arm, when they tell them that it is a randomised control trial-neither the physicians nor their patients could know who got what, the patients flatly refused to get into the control arm because they have all been sold to this clever marketing and publicity about plasma that's generated by media, that it's a magic drug. They ask why they should be in a placebo arm or a control arm or standard of care arm. India is probably at the risk of losing an opportunity, and the epidemic is still on, there are still enough patients, we still have a lot of untested drugs. This was an opportune time for us to test these drugs in a very well designed, well conducted Randomized Control Trials. I'm afraid that given all the circumstances, it would be extremely difficult to design, implement, execute and run high quality Randomized Control Trials with enough numbers in our

country. That is a challenge which our policymakers, researchers, and physicians must accept.

Sandhya Srinivasan: *Itoluzumab was recently approved after a phase 2 trial, without undergoing a phase three trial for its safety and efficacy in COVID-19. What is the evidence in support of this drug in this disease?*

Dr SP Kalantri: The drug Itolizumab is used when patients infected with coronavirus enter into their second or third week of illness. They are seriously ill patients, they are in ICU, many of them are in mechanical ventilators. During this time they are probably experiencing a cytokine storm. By cytokine storm, we mean that these people's defence systems suddenly got extremely angry, and are trying to get rid of the virus. In trying to do so, it is causing more harm than good so far as the body is concerned. It's possible that if the block is hyperactive, the immune system is very angry, and we try to calm it down by certain drugs, the patients might recover. On paper, it looks very good. Logically, the concept looks very appealing. This drug company launched an extremely small phase II clinical trial, and enrolled only 30 individuals. 10 of them were controlled and 20 were in the drug group. Phase II trial is aimed at testing the safety of a drug and not efficacy of a drug. Based on only 30 individuals you can never be sure whether the drug has really worked or not. After a phase II trial, we need a large Randomized Control Trial, called phase III trial, in which, hundreds and thousands of individuals are randomized to these improved drugs. And then we say that, well, all things being equal, this novel drug proved to be superior to the conventional treatment. I cannot understand the hurry in according approval to this drug, based only on phase II trial, which was done only on a very small subset of 30 patients, where we still don't know based on this extremely small numbers, that if tomorrow, when this drug is applied in a real world scenario, whether it would help or hurt more. For that, we need phase III Randomized Control Trial. All over the world, evidence and experience show that often, drugs which proved to be extremely successful or look very promising in phase II trials, when they were tested in phase III trial, at least a third of these drugs failed, or they produced serious side effects, which was not apparent in phase II trial. So, two things are occurring. They're approving these drugs based on a very small data of just 30 odd patients and we have completely waived off the necessity of a phase III trial. We are now asking this drug company to generate an evidence based on phase IV trial, which is also called post-marketing surveillance, where it is expected to count all side effects and report them back to the government. Right now, a lot of hope and excitement has already been created by the drug, that this is a made in India drug, is a real discovery, and that you should climb to your rooftop, shout from there and break into a victory dance. Now it would be extremely difficult to convince physicians working in the ICU. When the patient asked them "doctor why are we not trying this drug on us?", to explain to them in the ICU situation that we are still not convinced about the efficacy of this drug, we still don't know whether it harms or else and typically in an Indian situation, where this drug is likely to lead to a lot of serious life threatening and potentially fatal infections. People can die because of infection

and sepsis created by this drug. We must ask ourselves that in an Indian scenario, in an Indian ICU, where the infection control programs are not as good and as efficient, would we subject our patients to the significant risks caused by serious life threatening infection caused by this step? Probably, ultimately, it would turn out to be a Pyrrhic victory. And probably our losses would be much, much more than the small gains that we are accruing by the use of these drugs in our ICU.

Sandhya Srinivasan: *What is wrong with this trial's sample size of 30?*

Dr SP Kalantri: Well, let me ask you a counter question. Why did the researchers, even Anthony Fauci, need thousands of odd individuals to prove that Remedesivir works? Why did the researchers ask 175 UK hospitals and recruit 5000 odd individuals to know that dexamethasone works. The WHO sponsored and funded solidarity trial is recruiting 15,000 individuals from 70 countries in the world to know whether hydroxychloroquine, remdesivir, dexamethasone and other antiviral drugs work or not. The strength of the trials often lies in its numbers. If we base our conclusions, and start designing our therapies based on just a small sample of 30 individuals, there is a huge element of chance. It's quite possible that these patients might have improved if left on their own, as well, if we had sampled more individuals. A small sample of 30-50 or 100 is okay for a phase II trial. We're interested in knowing if the drug is safe. We're not interested in knowing whether the drug works or not, or is it really effective, or does it really cut down the mortality. You need a phase III trial. Bypassing a phase III trial and using a phase II trial on the basis of only 30 individuals makes no clinical sense at all. It's almost like replacing a 5 day cricket Test match with a 20-20 format and in the 20-20 format slock overs, apply a Duckworth Lewis to stop the match and say that we have won the match. This is neither cricket nor science.

Sandhya Srinivasan: *Under what regulation are these therapies being approved for COVID-19?*

Dr SP Kalantri: These guidelines were formed by the World Health Organization in 2016 after the Ebola outbreak, and they are called MEURI guidelines. MEURI stands for Monitored Emergency Use of Unregistered and Investigational Interventions. According to these guidelines, the physicians might use a drug or an intervention under very special circumstances. What are those circumstances? First, the disease has to be extremely serious or the situation, extremely desperate. The conditions should be life threatening. Second, there aren't enough proven drugs available in the country to fight against this particular disorder. Third, there isn't enough evidence based on either animal data or previous research about safety of this drug. Fourth, the drug should have been approved by the National Scientific Advisory Committee. Fifth, the drug should have been approved by the Institutional Ethics Committee. Sixth, you've informed the patients well in advance and taken their informed consents. Seventh, you monitor these patients to see if they will encounter any adverse event which occurs after the drug is administered. It is sometimes

reasonable to give an emergency permission, or off label or unproven or untested medicine, provided all these seven guidelines are being followed. Already, we have remdesivir and dexamethasone, which have shown to either reduce mortality or cut down hospital stay. What was the hurry in giving emergency approval to these drugs on extremely thin evidence, which makes a complete mockery of statistics and clinical trials based on just a small sample of 30 individuals or 100 individuals from 10 or 12 major hospitals. As of now, India has close to 900,000 patients infected with COVID-19. We have close to about 26,000 deaths because of COVID-19. We have 550 major medical schools in the country. We have major premier institutions in the country like AIIMS, PGI, JIPMER, Lady Hardinge, the four primary institutions in Mumbai, AFMC in Pune, and in down south, you have St. John's in Bangalore, CMC in vellore, JIPMER in Pondicherry. Why are these premier institutions in the country not able to enroll enough patients for high quality Randomized Control Trials and generate evidence from our own numbers, from our own communities? Instead, we are looking at extremely thin evidence generated by pharma companies. If we put ourselves into the shoes of a common man, we'll be able to answer a question that, in a country of 1.4 billion people, are you giving me a drug which was tested only on 30 individuals? Why were you not able to enroll about 1000-2000 individuals and if countries like you Europe and the United States are capable of doing that, why couldn't our country, with such premier institutions with people with outstanding clinical research, outstanding concepts of designing large, simple trials, why is this country is falling abysmally short of generating an evidence which matters most at this point.

Sandhya Srinivasan: *The WHO MEURI guidelines have been included in the ICMR's 2017 ethical guidelines for research. But they have not been applied to these drugs being used for COVID-19. The DCGI approved them for restricted emergency use in COVID-19. What does this mean?*

Dr SP Kalantri: Well, the point is, approval for restricted emergency use. The way the Favipiravir has been approved for these patients for mild illness, the guidelines apply to conditions where the patients are desperately ill, i.e., if they are in the ICU, probably the mortality rates are extremely high and The doctors are very desperate, the families are extremely disturbed there. Now, you want to try almost everything that might come on your way to save the patient. What is the point in approving Favipiravir where the patients have just small fever, headaches, body ache, and this fever would run its own course, most of the patients are destined to do better on their own. So what was the point in giving an emergency approval as if the mild COVID illness is a life threatening illness that might kill the patient? Similarly, in a way, I would still agree that if we are giving approvals for drugs, make sure that you ask these companies whether it has launched, well designed, large scale, well powered Randomized Control Trials. By passing these large and well designed Randomized Control Trials using just a handful of patients, and very cleverly and aggressively marketing drugs and saying that these drugs "cost only 34,000 rupees to an individual patient", it's an extremely sorry state of affairs.

Sandhya Srinivasan: *So what you're saying is that these drugs are being approved on the basis of no evidence, on the basis of small sample sizes, such Itolizumab – essentially, on the basis of very weak trials?*

Dr SP Kalantri: For Itolizumab, a clinical study has been published from Italy in a journal called Clinical Infectious Diseases, which has compared the efficacy of a Itloizumab's cousin called Tocilizumab in seriously ill COVID-19 patients. The study reports that although this drug has been able to cut down mortality, half the patients who were given this drug there have serious hospital infections. Many of them had ventilator associated pneumonia. You ask any intensivist working in an Indian ICU, how dreadful this hospital acquired infections are, how extremely serious this ventilator associated pneumonia are, and try hard as we might, it is extremely difficult to salvage the patients lives in our ICUs. Once they go on to the stage of developing ventilator associated pneumonia, they're on ventilators for weeks and we keep on pumping more antibiotics till we fall short of almost all antibiotics and this patient develops multi organ failure and dies. Today, in the Indian situation, where our ICU has a lot of problems in terms of resources, expertise, skills, manpower (particularly in tier II and tier III cities) where the infection rates are quite high, should we allow our ICU patients to be subjected to this adverse risk of serious life threatening infection caused by itolizumab? Shouldn't we tell these people that this could cut both ways or should we just tell them that this novel drug, which has just arrived in July 2020 would probably help almost every patient?

Sandhya Srinivasan: *These drugs have been approved for restricted emergency use. How does restrictive emergency use contribute to the research evidence in the drug?*

Dr SP Kalantri: Well, far from it. It does not constitute any research evidence. The World Health Organization and ICMR is giving doctors some time. We are pleading that situations are extremely desperate and chaotic, there are life and death issues, we have nothing to put our hands on, and so, let us at least try it out as a life saving measure. Nothing wrong with that. It is basically the doctors duty to make every effort to save a patient's life. But this doesn't constitute research. I strongly believe that even during pandemic times, when the situations are so chaotic, so complex, so demanding and so challenging, we need to have well designed Randomized Control Trials. If we do not do those Randomized Control Trials, for example, God willing, if we are able to conquer COVID-19, and it hits us again a year later, we will not have learned anything from this pandemic. We'll be exactly in the same position as we were about a year back and we would have failed to generate concrete evidence on the efficacy and safety of this drug. So, the times are opportune and although a situation is very desperate, we must design Randomized Control Trials and for once and all, say that, this drug works or doesn't work. For example, we learned hydroxychloroquine doesn't work, full stop. Now it's no longer being used in ICU. But had this RCT not been done, probably hydroxychloroquine would have been used in almost every patient who is

infected, who's exposed, who was not exposed, who is at risk or is not at risk of COVID-19. So, that is a great beauty of a well designed Randomized Control Trial, that they give solid evidence to base your practice on. Once you apply that evidence for the care of your individual patient, it is ultimately the patient, community, and the nation benefits.

Sandhya Srinivasan: *Do the regulations under which the drugs are being used right now, require the patient's be informed of the investigational nature of the drug and give their consent to its use?*

Dr SP Kalantri: From a very pragmatic point of view, it is nearly impossible to get a true informed consent from an ICU COVID-19 patient in any ICU today. Look at these patients. They are seriously ill, they're hypoxic, they're not able to understand what you are saying, their brain is not getting enough oxygen. Many of them have a tube in their trachea or windpipe. Many of them are on mechanical ventilators and life support systems. Added to that there are no relatives around because in ICUs, the patient's relatives are not permitted, be it in the ICU or even within the vicinity of the hospital. Given the situation when your patient is just not in the right frame to understand what you are saying, or he is so sick that your words just don't enter his or her brain, how valid are these informed consents? Informed consent in desperately ill ICU patients, when the patient's relatives are not around and the patients are seriously sick, are simply not valid. One might try to take the video consent from the relatives, but during those desperate situations, it's quite possible that the relatives would almost always say that, “Doctor, whatever best you can do you do for your patients. Please don't bombard us with so many facts, numbers and data, and the jargon, which we clearly don't understand”. They don't want to hear. All that they want to do is to go ahead with the new drug that’s being tried. The moment you say that, we don't know whether the patient would get this drug or or he might not benefit, or we don't know whether it works or harms, even the doctor patient relationship will seriously be compromised and that trust will erode. There are huge challenges in obtaining true informed consent in an ICU situation where the patients are seriously ill, and the disease is probably going to take an extremely serious turn. Even as a physician, I'm afraid, I don't have an answer, as to how to get true informed consent.

Sandhya Srinivasan: *Thank you very much, Dr Kalantri, for giving us an overview of the quality of evidence for the various therapies being used for COVID-19 in India. As you have pointed out, these drugs are unproven, and can have their risks. They are also very expensive. Still, doctors are prescribing them. Patients and their families are desperate to recover from this disease that can kill. They are also reluctant to oppose a doctor’s advice. And finally, the regulators have not taken any action to prevent such unethical practices on the part of pharma companies and the medical profession.*

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