COVID-19 in South Asia - A Practitioner's Workshop: Part 2

Transcription begins

Mittal Institute: And we're live. And Satchit, we're live. You can start this off.

Satchit Balsari: We'll wait a couple of minutes before starting.

Mittal Institute: Sure.

Satchit Balsari: Good evening and welcome to the second panel in our series hosted by Swasth Community Science Alliance and the Lakshmi Mittal and Family South Asia Institute, Harvard. These panels as several of you are aware are focussed at field practitioners, channel practitioners in rural and semi-urban settings across South Asia. And the panels are recorded and pushed out through YouTube links to various institutions across the region, after they are recorded. The first panel, to remind you, I'll drop a link in the chat, was focussed on these challenges around oxygenation and ventilation in resource-poor settings where there is no reliable power to even use the oxygen concentrators that have been distributed. Or if oxygen cylinders are to be brought in, there isn't necessarily the transport infrastructure available to make it possible to deliver the large volumes of oxygen that was mobilized across India. And of course, the challenges with ventilation when you don't have the right kind of training as soon as you move away from urban centers, even if equipment were donated.

This second panel today led by Dr. Amita Sudhir, emergency physician and Residency Program Director of the University of Virginia, focuses on high-value therapeutics. The response to COVID-19 in South Asia and across many countries around the world has been marred with misinformation and tremendous confusion around what works, what doesn't work. The sort of, battle around the use of ivermectin continues to rage as we host this panel. So we're hoping to benefit from some really brilliant physicians, scientists at the forefront of the COVID-19 response from around the world, to hopefully reach consensus on what works and what does not in treating COVID-19. I'm going to give away a little secret. Not much has changed since April 2020. Over to you Dr. Sudhir.

Amita Sudhir: Good evening and thank you all for joining us. I'm really excited about this discussion with our extremely qualified panelists. I'd just like to take a moment to introduce them. Dr. Shitij Arora is an Associate Professor in Medicine at the Albert Einstein College of Medicine in New York. He identified early in the pandemic that a subset of the patients may benefit from steroids and he worked on institution-wide protocol guiding steroid use in COVID. His research work more recently has been focussed on identifying prognostic markers of corticosteroid response in COVID. And he also leads the mycotic infections in COVID-19 registry which is studying factors associated with fungal infections in COVID-19. He is a member of the Swasth Community Science Alliance. Then we have Dr. Priya Nori who is also at Albert Einstein, an Associate Professor of Medicine in Infectious Disease and she directs the Antimicrobial Stewardship and Monoclonal Antibody Infusion Programs. Her research is the area of bacterial and fungal co-infections in COVID-19 patients. Dr. Raj Gandhi is an infectious diseases physician and the Director of HIV Clinical Services and Education at Massachusetts General Hospital in Boston. He is the Co-Director of the Harvard Center for AIDS Research and Professor of Medicine at Harvard Medical School. He is also the member of

NIH and Infectious Disease Society of America COVID-19 Treatment Guidelines Panel. And I'm going to be your moderator today. As Dr. Balsari said I'm an Associate Professor of Emergency Medicine at the University of Virginia. And I've been involved in writing COVID treatment guidelines since the beginning of the pandemic.

So we're going to start with maybe, talking a little bit about steroids which are extremely life-saving treatment but also a double-edged sword. So, Dr. Arora could you talk to us about the correct duration and dosing of dexamethasone in COVID.

Shitij Arora: Yes, Thank you Amita. Thank you Mittal Institute, co-panelists, thank you everyone for arranging this and to everybody who has joined. Steroids, so far, remain the most meaningful treatment that we are giving to critically ill patients with COVID-19. And the dose and the duration has been studied. It was guided first by the recovery trial. They used 6 milligrams of dexamethasone for a period of 10 days which is about 40 milligrams of prednisone equivalent. And since then there has been more trials looking at other steroids. WHO published this entire meta-analysis and they had about 7 trials in it and they looked at dexamethasone, methylprednisolone and hydrocortisone and they did not find that this mortality benefit was a drug specific effect, it was more of a class specific effect. So the equivalent dose of 6 milligrams of dexamethasone would be useful in this patient population and the duration would be anywhere from 7 to 10 days. There is some evidence gathering now that even shorter durations might be helpful. But yes, there is absolutely no need for doses larger than that and for duration longer than that which like you correctly said would only lead to more adverse events.

Amita Sudhir: So, what is the benefit of dexamethasone in these patients?

Shitij Arora: So, steroids in general, once the patients are in the phase of hyper-inflammatory phenotype which has been termed syndrome cytokine storm syndrome but, once patients are in that phase, steroids have a huge immunomodulatory effect and by reducing that cascade of cytokines, end organ damage is less. Now, if there was some notion earlier that dexamethasone was used in recovery and maybe this effect is specific to dexamethasone but the rationale behind that was that dexamethasone is a fairly long-acting steroid, so you know, if it's on for 36 hours there is not much rebound inflammation and this lack of rebound inflammation was attributed to somehow improving outcomes. But that hasn't been found to be true in all the literature that has been published since. And as a matter of fact, some of the research that we did, we did see rebound inflammation once steroids are interrupted or stopped. But in the patients who have this rebound CRP once inflammation is stopped, the outcomes were not much different than the patients who did not have that rebound in CRP. There has been a practice, I'm aware in India where CRPs are trended and if CRP continues to rise, another course of steroids are given for another couple of weeks and I think that's not based on scientific evidence.

Amita Sudhir: So with respect to outpatient vs inpatient, or just in general categorization of COVID patients, which subset of patients really benefit from dexamethasone or other steroids?

Shitij Arora: That's an excellent question Amita. So, the simplest way is that the sickest patients are most likely to benefit. And the sickest patients are the ones who have high oxygen requirements, have hypoxia or mechanically… invasive or non-invasive mechanical ventilation is being offered. Another way to assess which patients are sick or

belong to that sicker phenotype are the ones who have high inflammatory markers and C-reactive protein has emerged as one of those inflammatory markers which can identify that sick patient population. But I think one of the major messaging that got lost in this, was yes, steroids will benefit the sickest patients but there is a potential to harm, and seriously harm patients who are not sick enough. And I think that got lost in translation somewhere which ended up… Somehow there was this theory that there is a phase of viraemia then there is a phase of progressive severe inflammation. So everybody who is given steroids early, the inflammation would be less going forward and that's what probably led to this rampant use of steroids and I think, it's very important to know that if the patients are not sick enough which means if they're not hypoxic or if they don't have those high inflammatory markers, particularly CRP the litany of other tests might not be really useful. Steroids have the potential to immensely harm and I think that distinction is very important to make.

Amita Sudhir: So in general, especially without the ability to get a CRP or test for some other markers perhaps of who will benefit, would you say a simple decision point is if they're on oxygen, they might benefit from steroids. If they are not, then do not given them steroids.

Shitij Arora: Absolutely. If the patients are hypoxic, there is a role for steroids. If they are not, steroids are more likely to harm than benefit. So they should absolutely be avoided.

Amita Sudhir: And you alluded to this a little bit earlier, but there is no benefit to longer courses of steroids. What are kind of the downsides of that or are there any patients who would benefit from longer courses and what is the evidence there?

Shitij Arora: So, I don't think there is any specific category of patients who would benefit from longer courses. So, the short answer is no. There is absolutely no indication for longer courses of steroids. Potential for harm, it's huge and with the significant increase in mucormycosis that we have seen with 40,000 cases now being reported, cosmic study group from India they actually reported that about one-fifth of the 2,800 patients who were in their study, got steroids for longer than 10 days. And a lot of them were getting high doses of steroids longer than 10 days. So there is clearly evidence gathering now that there is serious harm because mucormycosis has a lot of mortality associated. So, there is no patient category, which would benefit from longer courses.

Amita Sudhir: So, it's clear from what you're saying that steroids used in the right patients, there's definitely a mortality benefit, they are mainstay of inpatient therapy. What are other aspects of the optimal inpatient management of COVID patients?

Shitij Arora: So, a large majority of COVID patients really need just two things, and if they are inpatient, it means they're sick enough to meet the admission criteria, so they need oxygen and they need steroids. Anything out of these two categories, the benefit is not immense and it has to be counterbalanced with the risk for harm. One of the drugs that has emerged is Tocilizumab. Tocilizumab in addition to corticosteroids in patients with high inflammatory burden may reduce the mortality further. Other than this and prophylactic anticoagulation, prophylactic because now there is significant evidence suggesting that in severe critically ill patients therapeutic anticoagulation might actually be associated with increased mortality. So prophylactic anticoagulation along with these drugs is all - for the large majority, this is all that's needed.

Amita Sudhir: Okay. Thank you so much Dr. Arora. I'd like to move on to ask Dr. Nori, a few questions about monoclonal antibodies. So, could you tell us what the monoclonal antibody treatments are that are currently available, including which ones are approved for use in India.

Priya Nori: Sure, absolutely. Thank you. So, in the US there are basically at least … monoclonal antibody products that are authorized for the treatment of outpatients. So, non-hospitalized patients with early enough COVID-19 that antiviral medications are still beneficial. Translating that though to India, the couple of monoclonal antibodies that have received authorization from India's regulatory agencies include the Eli Lilly products which are bamlanivimab and etesevimab, and also the, we call it regeneron, but the casirivimab/indevimab. And so, the distinction there is very important because actually the former - the bamlanivimab or the combination bam-etesevimab is unlikely actually to have activity against the Delta variant or the Delta plus. And therefore, if monoclonal antibodies are sought in India as a treatment option for high-risk but early COVID patients, in that they're in somewhere within their first week of symptom onset, really, the focus should be on the casirivimab/indevimab product. This has received authorization in India as I stated, however, cost may be a substantial hurdle. In the United States, thankfully, these medications remain free for our patients. So, for where I practice and where Dr. Arora practices, in the Bronx, our patients are extremely poor and there's a lot of parallels between our community members and those in India. And so, our free medication goes extremely far in treating some of the hardest hit communities in the world.

However, unfortunately, the system is not such in India, the Central Government has not purchased and then distributed these doses to various states or municipalities. Rather the drug company distributors themselves have struck a deal with various distributors on the ground. And so, the cost currently to the average patient is something like, I believe, 60,000 Rupees. That is according to the paper, the Indian Express which just released something about monoclonal antibodies, I think, the end of June.

And so, this seems like a rather prohibitive fee for the average family or the average patient. Unfortunately, like steroids, monoclonal antibodies are among probably five… four or five life-saving medications. The data now on these agents is very strong. They substantially relieve the burden on hospitals. They keep the sickest patients out of the hospitals to recover at home. If given early enough, they can prevent the need for oxygen therapy, they can prevent the need for hospitalization and then all the downstream supply that Dr. Arora so nicely described. But again, cost is a major hurdle. I'm not sure honestly what the US Government has done. I've sent many queries as to what they plan to do about distributing our unused doses overseas but I know that the pharmaceutical companies themselves have distributed several hundreds of thousands of doses of these agents on the ground for use for free basically. The other agent that I didn't mention is the latest monoclonal antibody is actually a mono-therapeutic agent. It’s called zetruvimab. This one also does show a lot of potential against the Delta variant. We don't yet know about Delta plus. The data still remains to be seen. But GSK which is the pharmaceutical company in the US which holds the patent for this drug is rapidly seeking the authorization process with the Central Government of India to get this agent as well, on the ground. So, the bottom line about these is that, of the, what four or five monoclonals that we have available, only those last two are going to be of any use in India against the

variant with the mutations that are of concern. And also, costs can be quite an issue. But if there's some channel to obtain these pro bono or for free, that really should be sought out. But as it stands now, cost can be quite an issue.

Amita Sudhir: So, which patients are the ones who benefit from getting this treatment?

Priya Nori: Wonderful question. So, as it stands there's basically, I would say three groups of patients. So, one is the higher-risk outpatient. So, the person who is currently at home. Currently not sick enough to go to the hospital and receive oxygen, but has several high risk features. Certain age, a certain body mass index, diabetes which is so many of our citizens in India. Any chronic health condition really. And somewhere within the first day, Day 0 to Day 10 of their symptom onset, and this is because this is where the viral loads are extremely high on the order of probably several millions. The sooner you get to time zero**,** the better. The higher the benefit more than likely for the patient. So, that's the first type of patient.

The second type of patient is the hospitalized patient but something is immunologically defective about that patient. Specifically in terms of their B cell immunity. So perhaps they are cancer patients or they're on a medication that blocks proliferation of B cells or something like rituxan. And so, if they specifically lack that arm of their immune system, the benefit can be quite profound. And so, this is unpublished data as it stands but it was a pretty big deal in a press release that came out from Regeneron, the company that produces the combination casirivimab/indevimab. The third population, which again is kind of still press release data. We are eagerly awaiting, actually the published data but this is in terms of post exposure prophylaxis, specifically in high risk settings. So institutional settings, nursing homes, patients who've been exposed and who are at high risk for progression. The impact of monoclonals given in the prophylactic setting was also highly successful. So, these are kind of the three areas to focus. If we can get these to the right patients, just like steroids, if we can open up the access to these medications just like with the vaccines, they can be life saving. So, that's kind of the bottom line.

Amita Sudhir: And this is all in the outpatient subset of patients. So, once they're admitted to the hospital we're not looking at this treatment?

Priya Nori: So, the second group of patients - the hospitalized but immunologically compromised patients… So you know, an oncology ward let’s say. That type of patient actually does stand to benefit and quite robustly from monoclonal antibody treatment. Because basically what we're doing is we’re giving back the missing component. So they're not, after being exposed and becoming infected with COVID, they lack the ability to respond to that. Likewise, they probably lack the ability to mount a response effectively against the vaccine, so what we're doing there is we're giving them back the missing piece. And so, that's how it works in terms of hospitalized patients.

Amita Sudhir: Thank you for clarifying that. So, what are the logistics involved in giving these drugs? Is there cold chain? What kind of infusion staff do you need? Can they just be given in any clinic or they need to be in a specific setting?

Priya Nori: Yeah, great question. So, logistically much easier to give than let's say, the Pfizer vaccine. There's no cold chain issues. They do not require a deep freeze. The storage is basically in the several vials that come from the company in a regular, old two

to eight degrees centigrade storage. Once the medications are mixed… So remember these are, some of these are cocktails and so, once they are compounded together, you have about a several hours shelf life. Probably not more than about overnight or 12 hours or so. So, for instance, if you intend to give it to one patient and that patient doesn't show up and you want to give it to the next guy, that next guy better be available within a few hours. But otherwise we've not experienced the situation where we've had to discard massive amounts of doses, like… unfortunately like they've had to do with some of the mRNA vaccines. So much easier to give logistically.

The challenge in the United States which I don't believe will be the case in India, is that there are several regulatory hurdles about who can and cannot infuse the medication, in terms of nursing credentials, but you know those things are not… I would say, probably less of a challenge in India. I would assume that anyone who's trained to do so, can probably give it, especially considering an emergency situation. Of course, you want to maintain all the sterility that you would do, that you would do with any kind of chemo therapeutic or intravenous medication. And you would want to make sure that there's a monitored setting. The patient does not have to be on a cardiac monitor. There's no anticipated major side effects of concern. Actually, in the clinical trials these medications were very well tolerated with a low degree of side effects. Even lower than the placebo arms. But there is, at least in the US, there's a mandatory about one hour watch period to ensure that if the patient develops anaphylaxis or something to that effect, there's somebody watching. I can tell you that in our practice here, we've treated several thousands of patients and serious allergic reactions in probably under five patients.

Amita Sudhir: And could you just clarify one more time for our audience which of these monoclonals are effective against the variants and if they're available in India.

Priya Nori: Sure, I would be glad to. So thankfully, the one currently that is available in…or the one that is effective against the variants, is available in India and that is the Regeneron cocktail - the casirivimab/indevimab. That received authorization several months ago and it is being distributed on the ground through Roche, which is a separate company. There is another one, also proven to be effective, which is called sotrovimab, which is made by GSK - GlaxoSmithKline, and that is in the process of obtaining authorization. So hopefully within a short time, that will be also available, at least to those who can afford it.

Amita Sudhir: That would be great news. Thank you so much, Dr. Nori and over to you, Dr. Gandhi. So, since you've authored the IDSA Guidelines on COVID Management, what would you say are the mainstays of outpatient therapy for COVID patients.

Rajesh Gandhi: Thank you for inviting me and thank you for that question. Maybe what I'll try to do, if it works technically, I'll flash up a slide for just a minute. Let me just share my screen and you can tell me what you see. Are you seeing, what I hope you're seeing, which is a slide that says Management Across the COVID-19. I'm getting a thumbs up which I love to see.

And so this is really reiterating the same points that were made by Dr. Nori and Dr. Arora. But it really emphasizes one important lesson which is COVID-19 treatment is not a one-size-fit-all. It depends where your patient is along the spectrum as to what you use. Because something that might work well in one stage may be harmful in another stage

and that was the point that Dr. Arora was making and I would completely agree with that that point. So, the reason I put this up is your patients will range from asymptomatic, pre-symptomatic where they have a positive test but have no symptoms, to mild or moderate illness where they have some symptoms but don't yet have evidence of hypoxia, to severe disease when they have hypoxia and extensive, long inflitrous to critical disease. And the reason why that's important is we think that what's driving those phases are different. We think the viral replication is driving mild to moderate disease and therefore antivirals like those antibodies that Dr. Nori was talking about is most likely to be effective, predominantly in mild to moderate disease and high risk patients or as she said, in people who have some immune compromising illness. This severe disease or critical illness, even though inflammation appears to start early the benefit of a dexamethasone and all the anti-inflammatories is essentially once you're hypoxic. And that's why, it's critical to not give dexamethasone to someone is not hypoxic and unfortunately, I think we have all heard stories where patients were getting dexamethasone and other steroids, when they were not getting hypoxic and I do agree that that's harmful. The recovery trial, the one that established the role of dexamethasone in the people who weren't hypoxic but were in the hospital in the UK, those people who got dexamethasone were the ones who had a higher mortality. It wasn't — but the trend was in the wrong direction. Was really only once you're on oxygen and particularly when you're critically ill that people began to benefit. So, let me take the slide down now, just to try to answer your question.

So, those are the two dimensions I think, of how severe is the disease and what is your intervention. Is that an antiviral like an antibody or is it an anti-inflammatory. One thing I'll say before getting into the outpatient management is, who should you worry about with COVID-19. Remember that when someone gets symptomatic, it's usually at about one week after symptom onset that they begin to take a fork in the road, either they're going to get better at that point usually or some people will get worsening disease at about a week after symptom onset. The people I worry about are the people who developed shortness of breath, the people who developed confusion, the people who developed chest discomfort, progressive symptoms or if they're in a very high risk group. They're older, they have those comorbidities that we were talking about like diabetes, that's the people I worry about. If they have access to an oximeter and some people do, you ask them to, I would suggest, that they take their oxygen reading a couple of times a day on clean fingers, on warm fingers and if they drop below 95% specially 94, 93, 92, 91, that's when I begin to get worried. What is the intervention? Sadly, the intervention for mild to moderate disease, outpatient disease is essentially what we heard. It's symptomatic management. Making sure they stay well hydrated. Making sure that they don't take harmful medicines like dexamethasone. And if they have access to the antibodies I do think that antibodies as Dr. Nori said, I fully agree are both, prevent hospitalization and probably are life saving.

What is not recommended for those outpatients is dexamethasone, what is not recommended for those outpatients are drugs like hydroxyclorine, azithromycin etc. Those are the drugs that either haven't been shown to work where there's insufficient data to support their use. So, for most of your outpatients it's going to be symptomatic management and if you have access, monoclonal antibodies and then close monitoring. Watch them over that 7 to 8 days, 7 to 10 days after they get symptoms, to see what direction they're going in. Remember, most people will get better, probably 95% of people will get better on their own… 90 to 95%. It's that 10% who aren't going to get better that you want to catch early, get them in the hospital and then if they're in the

hospital, there's a couple of treatments to consider. I'll just say one word because we don't have a place for this elsewhere about drugs like Remdesivir. Once someone is in the hospital, now they're on oxygen, Remdesivir is a controversial drug. The reason why it's controversial is because there have not been trials that show that it reduces mortality. There's not been trials that show that it improves survival. In particular, the WHO solidarity study found no mortality benefit of Remdesivir. The reason why I still, in the United States, think there's a role for Remdesivir albeit at a limited role, is that it probably hastens time to recovery. It gets people back to being ready for discharge once they're in the hospital if they're on oxygen but it's a relatively small effect. So, I would prioritize it lower than dexamethasone which does improve mortality. But if you have access to it, limited to the people who are on oxygen, not yet on a ventilator, you may recall that spectrum of disease once they're on a ventilator they're probably past the beneficial phase of Remdesivir, because the viral replication has gone down.

So limited role, I certainly don't think it's as important as some of the other drugs. I think it has a role in people who aren't yet on a ventilator but are on oxygen. We heard a little bit about some other anti-inflammatories. I'll just very briefly say that dexamethasone is the bedrock. I would not give it for more than 10 days. If someone has worsening disease on dexamethasone, more and more oxygen requirement or they have excess inflammation, that's where you either can use Tocilizumab, if you have access to it or there's this class of drugs called JAK inhibitors, Junas kinase inhibitors. they're another anti-inflammatory they tempt down the cytokines. One of those drugs is called baricitinib, another is called tofacitinib, these are other anti-inflammatories to think of, if you have access to them in someone who is on oxygen getting worse with a lot of inflammation. And so, those are where I would put those drugs. And now we're going to be talking about some drugs that probably don't have a role so maybe I'll pause there and see if you want to go there next or where you want to go next.

Amita Sudhir: Well, would you mind talking just a little bit about whether there's a role for inhaled budesonide in the outpatient population.

Rajesh Gandhi: Sure. So inhaled budesonide is a steroid of course. It is used in asthma. It's used in chronic pulmonary disease. There have been two studies. I'm going to give you the specifics so that you can see that there is some evidence, but not definitive evidence for inhaled budesonide. The first was a study done in the UK, called the stoic trial, it was in about 140 people, outpatients with COVID-19, so not a gigantic study. Think about recovery that's got thousands of people. This had a 140 people. Adults, and these were adults, were randomized to either get usual care or to get inhaled budesonide, this inhaled steroids twice a day. They did find in this small study that people who got inhaled budesonide had a lower rate of going to needing urgent care visits. So it was 1% in the budesonide group, 14% in the usual care groups. So large effect but in a small population, and the benefit was on preventing urgent care.

There was a second, very large study called the principal trial, also done in the UK. They have an interim analysis reported. So this one had thousands of people. It had 750 people in the budesonide group and over 1,000 people in the usual care group. What they showed is a very small, tiny effect of budesonide hospitalization rates about 8.5% with budesonide, 10.3% in usual care. So, a very small effect and one that was not as large as the smaller study. So in my mind, unlike dexamethasone - a systemic steroid, I don't think budesonide is likely to be harmful. As to whether there's a benefit, if there is one, I think

it's rather small. But I think more information will come. So, inhaled steroids, I would definitely think of differently than systemic steroids, I would avoid systemic steroids. Inhaled budesonide - small role, perhaps, but not definitive.

Amita Sudhir: And are there any antivirals at all that have a role in the outpatient setting?

Rajesh Gandhi: So, those antibodies that Dr. Nori was talking about, those are essentially antivirals but unfortunately they have to be intravenously infused or there may be an option to give the Regeneron cocktail subcutaneously. There's not as much data with subcutaneous dosing but there's some pharmas connected data supporting it. There is no oral antiviral as of July 6, 2021. We need an oral antiviral. Hydroxychloroquine was reported to be an antiviral but does not show benefit either in the inpatient setting or the outpatient setting. There's other drugs that are reported to have antiviral effects, ivermectin being one of them. Also reported to have anti-inflammatory effects. No definitive role for ivermectin and trials are ongoing, but the trials thus far have not shown a definitive role for it. There are a couple of experimental antivirals that need, very much need to be fast tracked. We need those trials to complete like in weeks not months. One of them is called molnupiravir. This is an experimental antiviral that works by blocking viral replication. In a phase 2 study, showed some promise in terms of decreasing infectivity, decreasing the duration of how long you could culture the virus. But it was too small of a study. It was only about 200 people or so. To show a clinical benefit, phase 3 trials in the outpatient setting are ongoing. And then there's a couple of other oral antivirals that are being studied. One is looking at viral replication from Roche Atea and then another is a protease inhibitor. Protease inhibitors have revolutionized HIV therapy. There's a viral protease inhibitor that's entering studies now. Then, lastly, there's a blocker viral entry called camostat. The data on that, we'll see soon I think. We'll know in the next weeks or a month or so where that ends at. That's a viral entry inhibitor and so we'll see where that is. But today, unfortunately, beyond antibodies, no proven antivirals.

Amita Sudhir: So, thank you all for this great summary of the things that do work and some things that don't. What I'm really hearing is that if you want to save lives, get oxygen to the patients who need oxygen, get those patients steroids, but don't give them to the other patients and then, if possible monoclonal antibodies to the subset of patients that will benefit from them and those are really are life saving interventions. But there are a lot of things out there that are in common use that a lot of people believe in that there isn't great evidence for and you know, I'm hearing more and more about more studies coming out on ivermectin and some other medications. So, I think we'll take a few minutes to talk about some of those and we'll start with everyone's favorite ivermectin. I don't know if any of you would like to comment on what the state of the evidence is for ivermectin and why you believe it doesn't work at this point in time.

Rajesh Gandhi: I can start by saying that evidence as far as next. So there are some studies that have some methodological laws that have shown a benefit. There's other studies that have not shown a benefit. Some of the more rigorous studies, one that was in JAMA not long ago, showed no benefit of ivermectin. But there's uncertainty, let me put it that way, and when there's uncertainty I think it's best not to rush and we learned from hydroxychloroquine with last year. That there are potential harms to giving drugs. Now both ivermectin and hydroxychloroquine have relatively few harms but if there's not a benefit then you're exposing people to a drug. Giving them potentially false hope and you

may not, and in the case of hydroxychloroquine, you're not benefiting them. In the case of ivermectin, we don't know that there's a benefit. It's just too unsettled. It's just too uncertain. One lesson I do want to drop from my past is from the HIV world. Back in the 1980s and 90s, we gave a lot of drugs with a lot of unclear value, and it was only once trials came into place that we were able to distinguish a drug that did work from one that didn't work. And I would say the lesson from HIV is you can potentially do harm if you don't subject something to a trial because you don't make progress, you essentially don't know if something is or isn't working. Once trials became available for HIV, we made steady progress, it took years. Now with COVID-19, we'll make progress over weeks to months because it's a much more fast-paced disease that lasts for weeks not years. And so, if we can do those trials we will know, in the short order, whether ivermectin does or doesn't work. But I wouldn't use it until I had some data behind it, that was our lesson from last year.

Priya Nori: Dr. Gandhi, correct me if I'm wrong but aren't the doses that potentially have some antiviral impact much higher than actually what we are able to give in human beings or is currently listed in any of the, for instance, the ICMR Guidelines I believe state 200 micrograms per kilogram one time. So, based on what we know from the in vitro studies isn't that… just not nearly enough? Can you give me your expertise. Can you maybe comment on that.

Rajesh Gandhi: I share your concern that, in order to inhibit the virus, the SARS-CoV2 virus in vitro, you need a lot more ivermectin than you can feasibly get into a person. So that's why, I think, a lot of us have been not enthused about ivermectin's potential. People who are positive about ivermectin have been wondering about tissue levels, other things that are very theoretic, and so I would say, again, what we learned from hydroxychloroquine is, we can get an answer but we just need to do a comparative study and put this to rest once and for all. And if we give the drug without clinical benefit we're doing our patients a disservice. We know our primary responsibility is not to do harm. We've already talked about how it can do harm with dexamethasone. I would say that we should get an answer before using a drug. Same was true of zinc, vitamin C, there's a dozen different drugs that we tried, that we need evidence for so… But your point about the in vitro, the kind of levels that you can get, that we want, need a trial in order to support it. You can't base it on just theoretic reasons.

Shitij Arora: Yes, and with every trial that has been reported, starting with the epic trial which… the Colombians reported in JAMA, then a recent Argentinian trial which came out about three four days ago. Epic had 400 patients, this one had 500 patients. With every trial that has come out, in mild to moderate disease with COVID-19, ivermectin has failed. Failed in three outcomes in preventing hospitalizations, in preventing death, in preventing mechanical ventilation. So, every piece of information that has come out has just driven that nail in the coffin a little bit more for ivermectin but there are what, 23 trials ongoing. Medicine is full of surprises, you know, but data is eagerly awaited. But until then there is evidence to the contrary that ivermectin might not be helpful.

Amita Sudhir: Yeah, I think the other thing that's interesting is you know these studies on ivermectin for prophylaxis, you know, as we see that the pandemic is continuing for months and months and months, are you indefinitely going to take ivermectin every day? I mean that just doesn't seem like a practical approach, even if the evidence did exist. So, I think there's an element of just the impracticality of this as well. So, another drug that's

gotten a lot of attention recently is 2DG and Dr. Arora, I was hoping you could comment on… is there evidence for this medication? Should people be giving it?

Shitij Arora: So, they haven't… DRDO hasn't been published the findings yet. There is no preprint available but if you just look at the trial design of 2DG, a couple of things are very clear. They excluded patients with diabetes. They excluded patients with chronic kidney disease. They excluded patients with heart disease, malignancy. So, they excluded most of the patients who are likely to die from COVID. And when they state the outcome in the trial, they say that we are studying efficacy but they haven't really defined what that efficacy is. So whether that's shortened symptom burden that the patient feels. So, there are many uncertainties around the trial design and unless the preprint comes out, I think, I think it will be too early to say anything about it. There were a couple of papers, they were studied by Patanjali research group and they started the docking design and how 2DG interacts with the viral docking design. So, I have my reservations on that, but unless the preprint comes out, I think there is just not any evidence to suggest this might be useful.

Priya Nori: Also, just to add to that, they basically skipped all of the steps that one would normally take between in vitro studies and then clinical use. And so, none of that in between, whether it be actual clinical efficacy or safety or you know, dose response or virtually none of that exists to date. So, I would put this one in the category of don't even bother. It's not going to come through for us, basically in the timeframe that we need. It's unlikely that we're going to see this data or that it's going to be a positive study, in my opinion.

Amita Sudhir: What about antibiotics given to patients, either outpatients or inpatients without any concrete evidence of a bacterial infection? Is there a role for prophylaxis? Is there some anti inflammatory effects that may be helpful? Is there any role for them?

Raj Gandhi: I think that's about it. The been best studied in this regard, is azithromycin because we know that may have some anti-inflammatory effect. But there is data now both in inpatient setting and the outpatient setting that azithromycin does not improve outcomes. So, I would caution us all not to be using it for treatment of COVID. I think early in COVID, bacterial and super infections were relatively rare. They can occur when someone is further along in their course. But then you're creating the bacterial superinfection, you're not using that antibiotic to in any way change the course of the COVID. So, I would monitor patients who are hospitalized for bacterial superinfection but I would not be using anti bacterials for modulation of the immune system. We have better ways to do that and azithromycin did not really show that.

Shitij Arora: Yes, I completely agree and one of the trials which has come over and over again today is recovery, and it was recovery, in fact, who actually showed that azithromycin has no benefit. So, there is high quality evidence suggesting that azithromycin might not have a role.

Priya Nori: Speaking for some of the other antibiotics, antimicrobials. The tendency is to treat very sick patients up front at the time of their presentation with COVID. Also with antibiotics, thinking that they also have, you know, gram negative sepsis or some other bacterial component and that's why they're so sick. Well now, 20 months or more into this thing we know that COVID, that SARS-CoV-2 virus, on its own is sufficient to cause very severe illness and even death. You don't even have to add another pathogen to the

mix. And so now we have studies out of many countries, virtually any country that was a COVID hotspot, we have data now saying that co-infection at the time of presentation with COVID was less than 10% of patients, probably less than 5% of patients. And as Dr. Gandhi mentioned, it's only once the COVID part, the virus has left the system that the patient is still compromised due to organ failure and due to prolonged hospitalization that we start to see things like these other infections staph aureus, pseudomonas etc. We have to keep in mind our setting here, which is the epidemiology is already not… given antimicrobial resistance is so… ongoing, and potentially fueled even further by the COVID crisis, we're only going to be adding to that in India, if we throw lots of antibiotics at people and will never really get over this vicious circle of anti-microbial resistance that has unfortunately been very closely associated with India now for the past decade or so. I would say, go seek out the data, the data from many countries is very consistent that we're just not seeing these infections, these co-infections in the way that may have initially been anticipated.

Amita Sudhir: You bring up an extremely important point Dr. Nori, about the danger of antimicrobial resistance and you know, I think post pandemic we're going to be looking back on this time and really thinking about how we could have done things better, because we could be looking at some really significant problems in the future. I think Dr. Balsari has a question for all of you.

Satchit Balsari: Thank you for allowing me to… question for all the panelists and perhaps Dr. Gandhi we can benefit from your long years of experience in dealing with this challenge. You know, Dr. Nori was just alluding to the challenge of antibiotic prescription practices in India, and you know, India continues to contribute, very generously every year, to the global antibiotic resistance problem. This has been dealt with in countries, antibiotic stewardship is something that each of you clinically and in new research careers have been very immersed in. What are the lessons that we can learn from elsewhere in the world in terms of effective antibiotic stewardship that can perhaps be applied to India at this moment where the medical fraternity has so let their peers around the world and their own patients down in India, by not just lack of antibiotic stewardship but just lack of science stewardship. Are there opportunities here, where we can apply the lessons that we've learned from the past couple of decades elsewhere in the world.

Raj Gandhi: I'll start but I think people should add in, because this is, both a simple and a complicated question. The simple aspect of this is that, we all share the same goal which is to make our patients better and that's kind of our touchstone. And what we've been talking about these last 50 minutes or so, are things that work but also things that can be harmful or things that just muddy the water or make things unclear which are things that have unproven benefits. I agree with you that stewardship of antibiotics and of antivirals and of our medicines is a key part of our professional and medical responsibility which is to use things where they work, but not to use things when we're uncertain or when they don't work. Early on in the pandemic, we wrote this editorial called 'Desperate Times Call for Temperate Measures', the point of that is that there is a harm to overusing drugs, there's a harm to using drugs that may not work, in terms of the side effects but also in terms of the financial costs, and just the false hope that it gives people. And then in the case of antimicrobial resistance, there's a downstream effect that affects not your own patient, the one who gets resistant but also people who acquire that drug resistant bacteria, drug resistant fungi. So you know, I think that's a probably an underemphasized point that you're making around how can we make stewardship the norm rather than the

exception around the world. I think that should be our goal, to kind of integrate stewardship into the best medical practices and I'm happy to have a conversation around how to do that. I'd love to hear from others on the panel.

Priya Nori: So, if I may just pigtail I guess, off your comments. I am an antibiotic steward and I think the number one place we can focus our efforts is in the outpatient setting. So what that means for India is, anywhere that's not within the four walls of the hospital, that's a separate piece, we have to tackle that at some point and we need help from the central government to say that, just like in the United States or in Western Europe and other countries, this has to be something that every hospital has to have a system of patrolling and monitoring their antibiotic use. But separate from that, let's start, just like on the block. Like our local, in the Bronx we call them bodegas, but in India there are these open-air markets where you can get like a bun, and you can get a soft drink and you can get antibiotics. You can, even get sometimes IV antibiotics. So, I was astonished to see that, one time I went to India, my cousin was injecting my aunt with amikacin that he, you know, bought at the local corner store. So our lens has to shift to see how we can get all those practices under control outside the hospital setting. We know from the US that that's really what is driving antibiotic resistance in this country. It's all what's happening in clinics, in urgent care centers, in dental practices and so if we could do something similar, apply that learned lesson to resource limited countries, I think that would be a great place to start. Just like what we saw with steroids, a lot of the antibiotic overuse was driven by patients, not even accessing acute care or the hospital, it was all done at home. So really, we need to get that under control.

Satchit Balsari: Thank you Dr. Nori. Back over to you, Dr. Sudhir.

Amita Sudhir: You know, there is also, I think, some other medications that are prescribed, that seem quite harmless like zinc and vitamin D. Do you all have any input on those, I mean, they're just over the counter, easily available medicines. They don't seem to have a big downside. So you think there is one?

Shitij Arora: One of our friends, Professor Mohanan said there is an opportunity cost to it, and as benign as something like zinc might seem, some of the initial data from our mucormycosis registries says that there could be some association with how invasive the fungal infection was in patients who were taking zinc as opposed to those who were not. And zinc is a micronutrient which the fungus loves. So, while it may appear that they're seemingly harmless, there is both an opportunity cost and as well as you know the adverse effects which we are just not aware of and given the lack of clear benefit, sticking with what we do, which is do no harm, I think it's best to avoid zinc supplements.

Amita Sudhir: And then there's a question in the chat about the role of prophylactic anticoagulation in outpatients. I think you already touched on that - inpatients in the inpatient setting but they're also asking about inpatients post discharge. Is there any role in either outpatients or post discharge inpatients?

Raj Gandhi: You know… Dr. Nori did you want to comment first, you look like you're gearing up.

Priya Nori: You go ahead.

Raj Gandhi: When I talk to my hematology colleagues, they say that there's some instances, so I wouldn't routinely give prophylactic anticoagulation to my outpatients, I agree with Dr. Arora that all inpatients should be getting prophylactic doses of anticoagulation. There's enough evidence that that should now be standard of care. But once people are ready to be discharged I think, then, unless they have some other condition for which they would ordinarily get prophylactic anticoagulation, and there are a few, our hematologist know what those are, I wouldn't give them prophylactic anticoagulation just because they had COVID. So, that's my own perspective prophylactic anticoagulation while they're hospitalized. Once they're discharged, no prophylactic anticoagulation, unless they have some other reason. You know some non-COVID related reason. That's my short answer.

Priya Nori: I think the same goes for things like asprin. I don't think that they've shown that something like an antiplatelet agent like aspirin provides any benefit to patients outside the hospital setting who don't have other cardiac indications for those drugs.

Shitij Arora: Some of these adaptive platform trials have been super helpful in answering these questions one by one and REMAP-CAP recently ticked off aspirin. I'm sure there are many more drugs to fall.

Amita Sudhir: Well, we have about two minutes left. So just as we're wrapping up, I'd like to address the question to Dr Gandhi. While HIV AIDS isn't technically a pandemic, it is a global epidemic of almost pandemic proportions and you've worked in this field for a long time. And so, I was wondering if you have any lessons for frontline providers and researchers, kind of overarching lessons from HIV, that we can apply to COVID going forward.

Raj Gandhi: So, I'll draw two lessons from my trivia. I'll lead it with the first but… people have asked, can you do with clinical trials during the pandemic. What the answer is, you must do clinical trials during the pandemic because the very definition of a pandemic is, you have a new pathogen for which you don't know what does and doesn't work, and that was the lesson of HIV, it's the lesson of COVID that you must do these trials in order to make any progress at all. And that's why, those of us who've been doing it, actually felt so strongly that we needed to follow that same approach for COVID. The other big lesson from HIV is that it's iterative. Dr. Balsara said that we haven't made that much progress in 15 months, there hasn't been enough progress in 15 months in therapy, I would agree, but it's iterative. So you develop a drug, in the era of HIV was AZT, then you develop another drug through D2C and then you combine them. And then you get to a tipping point, in HIV that tipping point was 1996, and it took years before we got to that tipping point. But once it tips, it tips very, very quickly and the same will happen with COVID. Sadly, because there is so much COVID around the world, if we invest in those trials to get ourselves one drug after another, until we get a combination or we get some approach that really changes the outcome meaningfully. Dexamethasone has helped. Antibodies have helped. I do think there's a role for some of these other immuno-modulators but it's largely going to be that iterative process where you build one, in essence, on top of another. So, those are the two lessons I've taken from HIV and I think we will make more rapid progress for the reasons I said, this disease it's got many more billion people and many more millions of people infected in much shorter of a time, and it's a global in a way that HIV has been but not to the same extent because of its roots of transmission, but the progress will be made in the same way. Just much more rapidly.

Amita Sudhir: Thank you and thank you so much to all three of our panelists. You've brought an amazing amount of clarity to what has been a very dense amount of overwhelming information. As someone who's been caring for COVID patients, for the last 16 months, I can say that you have made all of these treatments much more easy to understand and to understand the rationale behind them. I think the take home lesson for all of us is to really evaluate the evidence critically, to remember that you know, there are a lot of preprint studies out there, there's a lot being published. But to really look at the quality of the evidence and whether it's applicable to the clinical setting we're working in, whether it's practical to apply and to remember that, after 16 months the treatment for this disease is quite simple. There have been some advances but we just need to remember that the basic things still work and to continue to do them. So, thank you so much. Really appreciate the wealth of information that you provided us.

Shitij Arora: Thank you.

Priya Nori: Thank you so much.

Satchit Balsari: Dr. Sudhir, thank you for hosting this panel. Thanks a lot.

Amita Sudhir: Thanks to our audience for joining.