Regional SARS-CoV-2 Variants and Their Impact on Inpatient Treatment

CMEO Podcast Transcript

Sai Praveen Haranath, MBBS, MPH, FCCP:

Hello and welcome. On behalf of CME Outfitters, I would like to welcome and thank you for joining us for the CMEO Snack, *Regional SARS-CoV-2 Variants and Their Impact on Inpatient Treatment*. This CMEO SNAC is supported by an independent educational grant from Gilead Sciences. This activity may include discussions of products or devices that are not currently labeled for use by the US Food and Drug Administration of the FDA, and the faculty have been informed of the responsibility to disclose to the audience if they will be discussing off-label or investigational uses, any uses not approved by the FDA of products or devices. I am Dr. Sai Haranath. I am a pulmonary and critical care doctor, and I work at Apollo Hospitals in Hyderabad, India with a large multi-specialty hospital group in its situation across India.

And the reason I'm doing this today is because of the fact that COVID was all over the world and we saw the brunt of it in terms of looking at both outpatients, inpatients, and very sick critical care patients. I'm joined by my distinguished colleague, Dr. Christina Mussini, and she will introduce herself.

Cristina Mussini, MD:

I'm Professor Cristina Mussini. I'm a professor of infectious diseases and the chief of the Department of Infectious Diseases at the University of Modena and Reggio Emilia. And I'm here probably because Italy was the second country that was hit by the pandemic and so we experience it like a shock. And so I think that it will be interesting to talk about COVID from two different perspectives, the European one and the Indian one.

Sai Praveen Haranath, MBBS, MPH, FCCP:

Absolutely. And to frame the discussion today, let me just review one learning objective in which we are going to analyze the regional differences in SARS-CoV-2 variants and that influence on the effectiveness of inpatient COVID-19 treatment strategies. And Cristina, if we were to think about the pandemic itself, it's almost a memory now, which people don't even remember about it. And almost thinking that it's probably important we do these CMEs at this time, because this is where we can remind ourselves of the learnings. And there's been a lot of information that has been gathered in the few years since the pandemic, and there's been shifts in variant dynamics, especially in different regions of the world.

What do you think are some of the most persistent misconceptions about COVID awareness, particularly in Italy, and what is it that's creating gaps between the patient and the clinician, and which of course in turn can impact effective disease management? And I'm more referring to the clinical things that you've seen. Of course, there's a lot of social media impact in all of this, but what is your clinical impact that you've seen because of the variants?

Cristina Mussini, MD:

I think that if we talk about SARS-CoV-2 misconception between patient and clinician, I think that since in all our countries in the US, as for example, in Italy, there is a new commission that will evaluate all the behavior and the political behavior at that time, in a way, trying to lower the attention on this virus. And also there is a sort of idea of removing from the public idea the presence of COVID. Now, for example, we are talking only about

influenza, while we have both influenza and COVID. And among the misconception, we have that natural immunity provides superior and efficient protection without vaccination. And this is something that we have seen that the vaccination plus the natural immunity is really the best one because the natural immunity is a booster for the vaccine. And also the idea of emerging variants are more severe and current vaccine are ineffective.

This is something that is just to ... There are people who want to threat the population, and this is absolutely untrue because we will see that emerging variants since Omicron are still under the efficacy of the vaccination. And also, they don't replicate very much in the lower respiratory tract. So we don't see severe pneumonia anymore. And lastly, that long COVID is not a real or serious medical condition, that is something that is absolutely not true. The serious one is rare, is not described as often as during the pandemic, but still it has a big impact on the everyday life of people with COVID.

Sai Praveen Haranath, MBBS, MPH, FCCP:

Right, that's very interesting. Thank you for sharing that. So what I'm hearing you say is that there are still plenty of people who are not aware of the benefits of vaccines, who are still not aware of the benefits of getting treatment, even though the variants are mild. And of course, long COVID is a real thing. And thank you for those perspectives. And I'm just going to very briefly review the evolutionary trajectory of the COVID strains. We know they started in Wuhan, then became the Delta, then in 22 became the Omicron. And if you look at the way the current one, I believe it's Stratus or Nimbus is the one that's there. I think the names don't matter. Ultimately, we do know that there is a trophism for the respiratory tract and other parts of the human body.

And I think it'll be interesting, Cristina, if you can share with me, what do you think are the genotype variants that the COVID virus has undergone? And could you give an overview of the virus itself? And has it really undergone drastic changes over the years? And if you want to juxtapose that to what the influenza virus does, just so people have a context of that this is new or this is different, or is it what all viruses do?

Cristina Mussini, MD:

The problem with viruses is if our immune system have seen them before in the history of human being. So that's the problem of the variability of the viruses is something that, for example, affects very much influenza A. The problem is that until we have small variation, so that is named antigen drift, there's no problem. We can have a little more severe than the year before, but in general, our immune system recognize the antigen on the surface of influenza, and it's okay. While the situation is completely different, if we have a complete rearrangement of the surface antigen named antigen shift, and this antigen shift transform influenza A, because this is possible only with influenza A, because influenza A could affect human and animals. And the new virus with the antigen shift usually come from spillover from the animals to the human. And since our immune system, as it happened with SARS-CoV-2, have never seen this new virus, it's a disaster because we are defenseless towards this virus.

And if we look at the biological mechanism of SARS-CoV-2, we see that if we look at the structure of the virus, we have the envelope with all the spikes, glycoprotein, we have the membrane protein, and we have also the nucleocapsid, and we have the RNA inside. What's happened with how it could enter the cells? It enters using AC2, that is the Angiotensin-Converting Enzyme receptor two, and it's obligate to enter through this receptor. The problem is that this receptor is in a lot of cells, really in many cells. So in nasal epithelium, bronchial

epithelium, type two alveolar cells, small intestine, heart and kidney. And this, in a way creates, like it happens for HIV, for example, an immediate distribution of this virus in the human body, especially in the lungs because we have to know that especially the variants until before Omicron, they can multiply in the lung, especially in the lung, while now it is mostly in the upper respiratory tract.

And this with the new variants like Omicron or Stratus Nimbus, these variants replicating, especially in the upper respiratory tract, are much more infectious than it's easier to transmit it. So more people are involved, but we have less severe case.

Sai Praveen Haranath, MBBS, MPH, FCCP:

Great, that's amazing. Thank you so much for that overview. I almost recollected my med school days, so thank you so much for reminding me about the basics. And if you look at the CoV-2 virus, SARS-CoV-2 virus, there's been multiple trends with the new genetic variants, and for each year there's been something different. And like you mentioned already, some of the names, when we started off in, I would say 2019, we can all go back to thinking what we were actually doing at that time when the pandemic got announced. We had the Wuhan HU2 original, I think it was HU1, I think it was called, and then it went on in 2020 to the descendants of that, the original one. And then in 2021, we had the alpha, the beta, and then we had the delta, and then the 2022 onwards, I think things started slowing down a bit, the BA1, the BA2, the BA4 and five, and 23, we had the XBB, and this is for folks who are interested in trivia.

So these names really don't matter, they're just names we gave it to them. And 24 is the JN1, and now I'm just skipping a few. Currently, we have the XFG, so it's going to keep changing. But what's important, I think, and interesting to understand is that this variant timeline is not going to go away. The virus is going to remain and it'll be good to know, and I'm hoping it disseminates into an innocuous common cold situation and goes away, but we don't know. So that's one of the reasons we have to keep reminding ourselves on how to tackle it because if we can pick it up early, detect the evaluation and the treatment plan early, we could probably save a few lives. So I think it's important also to consider the unique region-specific waves that can influence downstream patient management. And today it probably doesn't matter so much because they're fairly mild.

However, the variants are there and we have to keep tracking and we really have to keep looking at what's coming where. And Cristina, recently, what have you seen in Italy in terms of a variant spike pattern? Because in India, we are doing some limited amount of genotype. I think there are some institutions in the governmental area that are actually looking at this and tracking it, but I guess in the private sector, we really aren't doing any more really genotyping at all that I know of. It's not done at a routine basis at all. How about what's happening in Modena and your area?

Cristina Mussini, MD:

No, these are national data from the Ministry of Health. Obviously, the number of nasal swabs has decreased greatly. So the idea is what we have is if you look at the graph, if you look at the slide, you see that what is happening now, it's what happened from the beginning of the pandemic, that certain variant in this case is XFG starts and then in a few months it takes over. And from May when it was 10, 20%, it has increased along the month. And now, in October, you see it was largely the predominant one. And if you look at the different sub lineage of this variant, you see that there are many. You see in this beautiful slide, it's like a piece of art and you

see it's the XFG, but it has so many different lineage that you can see how heterogeneous it is, but still not severe.

This doesn't mean that you don't have for sure a severe clinical picture because it depends mostly on your baseline situation, on your clinical situation, but still we are not seeing and not even foreseeing ... I completely agree with you that it's going to stay, it's not going away this virus, but for now, there is no clue that it's going to undergo antigenic shift.

Sai Praveen Haranath, MBBS, MPH, FCCP:

Got it. And I guess in my area, the variant spikes have been, fortunately, nothing that is of concern. Most of them have been either for monitoring or under something of interest. JN1 is a variant of interest, and under monitoring, we've had the XFG, the XCC, et cetera. So there's a few of those out there and these will keep changing.

Cristina Mussini, MD:

Yes. So now to ground us in strategies to take all unique clinical scenarios and how and where to act, let's walk through a case scenario. So Sai, tell us about the patient.

Sai Praveen Haranath, MBBS, MPH, FCCP:

So it's interesting, and I think it's fun that we're able to have this conversation, and healthcare is so universal that way, that we're able to actually understand and really come up with a treatment plan. The patient could be anywhere. And we know there's such a universal global travel that you do need... Patients can be in one country today and another, the next day. And it's important to understand that most of the care patterns are about the same, but let's assume that we do have this patient. Some of the cases I'm going to discuss right now is based on our experience of seeing similar cases, which I'm sure you have too. And this is a young woman. PW is a 29-year-old woman. She has rheumatoid arthritis, and she's been on just some maintenance type of prednisone, which is not something you use for a long-term, but she had just been diagnosed and they're testing out the meds.

And then she came up one day with having had a couple of days of fever, a little bit of cough and chills. And then it wasn't getting better. So she ended up in the emergency room like most of the people do if it's say a Friday night, they're going to end up in the ER. And she was febrile, 101.8 Fahrenheit or 38.8 centigrade, and she was tachycardic as expected, 104. Blood pressure was 104/55, which is borderline, not too low, not too high. And she was breathing a little bit faster, about 18 breaths a minute. Saturation was about 97% of room air, which is normal. So then the emergency room physicians went ahead and did all the usual testing, examination. And the exam was pretty unremarkable except that she was warm and looking a little uncomfortable. They did some blood work and the blood work showed WBC count at the upper limit of 11,000.

And there was about a neutrophil predominance of 70% and 12% lymphocytes, and the absolute lymphocyte count is about 0.9. There was zero eosinophils, which is an interesting thing to keep an eye on. Luckily, she was not that dehydrated yet. The chemistries were normal, the kidney function was normal. The CRP was mildly elevated, and the test X-ray that they did was normal. So she got admitted because they were trying to figure out what else could be going on. She was a little immunosuppressed and they didn't want to take a chance. And it turned out that they ran the COVID test, of course, and that came back positive. They were thinking influenza,

influenza was negative, and they were not sure how she picked it up, but then she got admitted to the hospital. And when she got admitted to the hospital, the initial features were that the shortness of breath was getting worse.

Her oxygen saturation was slowly declining. It came to 92, and the X-ray was now showing some changes, a little bit of bilateral consolidation changes. They did put her on oxygen, which is the next thing to do. And given that she was COVID positive, young woman, they went ahead and gave about six milligrams of IV dexamethasone. So I'll just pause there, Cristina, and just get your commentary on, does this case feel atypical to you or does this feel just exactly how you would look at all the patients from five years ago or yesterday? Would they all look similar? And then we can jump a little bit deeper into what happened to this patient.

Cristina Mussini, MD:

I think that since she was a patient at risk of having a clinical worsening, I think that I would have treated her with antivirals. Depending on the drug-drug interaction, in Italy, we could use Paxlovid, also Nirmatrelvir-ritonavir, or remdesivir since she's admitted, she could do also remdesivir. So I think that it's, especially because if she's on prednisone, the interaction with ritonavir could generate cushing's syndrome. And so usually we don't use it. I'm an HIV doctor, and we have seen so many cushing's syndrome even with steroids, inhale steroids, or even with cream So probably I would have used remdesivir. And what would you-

Sai Praveen Haranath, MBBS, MPH, FCCP:

Interesting.

Cristina Mussini, MD:

Would you use the antiviral at this very beginning?

Sai Praveen Haranath, MBBS, MPH, FCCP:

I think I would. In this situation, I would. And then I think the other thing, of course, I think I would probably pick rimdesivir depending on how she's doing. The oral pills, sometimes it also depends on the availability of the medications. So for us, Paxlovid initially was at that time, at least now it's probably more available, but not always. Each geography is going to be different, so you really have to pick what you do. The other thing I would recommend everybody is to ... There are going to be institutions, and even if you're a private practitioner or smaller hospital, you will have these protocols published by your own societies and the global societies. So just download a copy and keep it. And there's plenty of online resources you can go to, to look at what needs to be done. In our hospital, for example, because we are 75 hospitals across India and 10,000 beds, we had to come up with a steering committee and really look at ...

We had a hundred versions of... Our protocol kept changing as the science evolved, and it was very helpful for people who were not keeping up with the latest. So it will be helpful to ... This CME is, of course, an example of what you could do to learn more, and some of the slides have good detail on what you could do. So jumping back into this patient, PW, so unfortunately she kept getting worse. Her saturation dropped to 85%, and then the CRP went quite high, to 160, and a single dose of tocilizumab was given, and they tried some non-invasive ventilation. They tried little, simple measures to leave things to get better, but didn't. So she ended up getting

intubated, and then they treat like ARDS. You use high PEEP, low tidal volume, and the learning point there, it's less than six ml per kilo, ideal body weight, not the actual body weight. And when that was done, they also had to do proning.

And proning, as you know, is helpful because most of your lung is in your back. And if you look at the images, in fact, the Italian pulmonologist, Dr. Luciano Gattinoni, who's no more, who actually showed that the lung is atypical in terms of its architecture. And in ARDS situations, if you put them prone, you can actually change the... Redistribute the ventilation perfusion better. And this is something that is well known to help. And in this case, it did help. And then you ended up with the lung mechanics improving over about a week's timeframe, oxygen requirement improved. And by the eighth to ninth day, got extubated to a nasal cannula. And by another 10th, 11th day, she got into room air and then got transferred to the ward for rehabilitation because now every day in the ICU you get weaker. So luckily she was young and the steroid dose was not too high, so she was able to do well.

If you look at the trajectory of her vital signs on the slide, you can see the decline in the oxygen. The febrile nature came down and obviously you have to keep a watch on your ventilator settings, et cetera. So I'm going to quickly ... The one interesting thing in this case was tocilizumab. Do you use that in Italy, Dr. Cristina? What is your comments on that?

Cristina Mussini, MD:

I was among the first to use it. I published also paper on Lancet Rheumatology about this because I could see from ... The Chinese were the first one in using it because there is a high bunch of IL-6, high concentration of IL-6, so the idea of using tocilizumab was good. And there was someone in Naples who started talking about tocilizumab at the very beginning. So after 20 days of the pandemic, in Italy, I started using it. I used most of the cases two doses, not just one dose. And I have to say that as also the RECOVERY trial showed there was a decrease of 30%. It's a long time that we don't use tocilizumab because the vast majority of our complication are maybe bacterial complication of a COVID or a patient who started with COPD or asthma or whatever, and they got COVID and they have a deterioration of the respiratory condition, so they don't need tocilizumab.

But we had great result with tocilizumab, I have to say. But also I did another of these CME with an American colleagues. They have the same results also with baricitinib that it's even easier because it's oral and it's cheaper.

Sai Praveen Haranath, MBBS, MPH, FCCP:

Absolutely, absolutely. And again, that again, to me, it drops down to the availability of the drug. If you don't have a stock of it, it's harder. Tocilizumab may be easier in some settings, but you're absolutely right, any of those would have worked. And the other things about this case that are important, I think, is the basic critical care because a lot of mortality that happens in any disease when they get to the critical care unit is not from the disease, it's from forgetting to keep the head of the bed elevated. So you decrease your chance of ventilator associated pneumonia. It's not taking care of the glucose level. It's not taking care of DVT prevention and prophylaxis. And of course, making sure that secondary infections are watched for and look for skincare. These are the common things.

And of course you have to make sure the patient's comfortable, especially when they're on such high settings on a ventilator, they may need adequate sedation, and oftentimes they may need paralytics too if there's going to

be a lot of proning involved, but all of those things can affect the muscles and the recovery takes longer. Now, one interesting point I think it'd be good to touch on is the anticoagulation. So anybody who's ill in a hospital needs prevention of blood clots with typically medication, some form of a low molecular weight heparin or any other product, and of our subcutaneous sequential compression devices, what we call the SCDs on the legs. However, there was some, I would say interesting data that in COVID you may need to use a higher dose early on, anticoagulation. I think now though the data has shown that if you're very sick, you don't use a higher dose. Would that be correct, Dr. Cristina?

Cristina Mussini, MD:

I think that at the beginning the idea was to treat everybody with a high dose of everything, but then we just came down to our senses, to common sense. So I think that it's much better to use the prophylaxis at the beginning. And then eventually if you have the demonstration of a pulmonary embolism, then you go to therapeutic doses.

Sai Praveen Haranath, MBBS, MPH, FCCP:

Sure. And in ICU, when you rotate, there's an acronym that we use, it's called FAST HUGS. The F is for feeding and algesia, et cetera, you can look it up. So it's an interesting thing for the listeners to remind themselves, especially if they don't do critical care on a regular basis. So I think we've looked at this interesting case, and if we were to really look at the variants ... So to me, the takeaways are that one, critical care is important. Identifying oxygen requirement, worsening is important early on. Intervening early with the steroid as well as the specific therapy to prevent the cytokine issues is the most important. Specific therapy for the virus is also important. And of course, keeping the family and the patient updated because everybody's going to be stressed in a time like this, and it's helpful to do that.

Of course, infection protection, personal protection, and reassuring your staff on that this is safe if you're doing it right, just like any other disease, is important. And I think you work in HIV and in the early time of HIV, people were afraid, early time of COVID, people were afraid, but I think now we have understood how things can be done well. So to me, the variant in this case, even if it was say an XFG or an NB.1.8.1, I don't think it would make that much of a difference in terms of the treatment, but if we were to look at that, what do you think, Dr. Cristina, if there was a different variant, do you think something should be done differently?

Cristina Mussini, MD:

Well, the problem is that it depends on the region you are living in because XFG is mostly in Europe and in America, while NB.1.8.1 is in Western Pacific, but let's see if you have one or the other, if there are differences. So WHO public health risk level low for both, vaccine effectiveness expected to remain affected in both. So I think that this, and also the severity, no increase versus prior variants in both. And then there are small differences like global prevalence looking at the geographical distribution, 71% of the sequences in the world belongs to XFG, while 15% of the sequencing belong to NB.1.8.1 and the other difference is about the transmissibility.

It has a moderate growth advantage, the XFG. It has a low H2 binding affinity and a highest relative growth rate while the NB.1.8.1 has a high H2 binding and 2.5 fold higher infectivity than a previous variant in that area. So I think that the most important thing is to look in the blue part with the key findings because as we said, since

both variants replicate in the upper respiratory tract, they have enhanced transmissibility, but not an increase in severity. The public health risk is low for both. Vaccine remain effective and consistent symptom profiles with prior Omicron variants. As I said, our life has completely changed since the arrive of Omicron variants.

Sai Praveen Haranath, MBBS, MPH, FCCP:

Very true. So really speaking, the actual management may not be very different. And if you look at all the guidelines out there for inpatient treatment, there's an interesting set of guidelines from the UK, from NICE, the IDSA from the US, ICMR from India, the WHO. And I think each one classifies the severity pretty much in a very similar way, in terms of using the respiratory rate or the oxygen saturation. And the first-line treatment for everybody is steroids. And if you look at those, and many of them have an antiviral in there, you can pick which one you want. And Dr. Cristina did mention the ones you're talking about. There's one interesting thing that we did in India was the awake proning, and there's a billion people, so you don't have that many ventilators. And it's improved very much now. The critical care infrastructure's improved a lot.

There's a lot more availability and training for this. And just a quick aside there, at Apollo hospitals, for example, in my hospital, we did a lot of remote monitoring. I do remote tele-intensive care. We were watching patients in ICUs in places which never had integrated patients. They would often transfer those patients, but they didn't have a chance at the time. And we were able to remotely monitor and take care of them. And I've been doing this for a long time in remote monitoring, but during the COVID time, it was really interesting where people quickly learned. And luckily the treatment patterns we are seeing, you can very quickly educate people on how to do it. But there are a few second-line treatments. This patient we discussed did get the second-line treatment, and we talked about tocilizumab as well as baricitinib, and these are in the guidelines. And the DVT prophylaxis is something we also talked about in terms of how we dose it.

And I think as we learn more and we look at the data over time, we will come up with more nuanced recommendations. But as of now, what we've discussed is the simplistic way to look at it. And if we were to look at what we've talked about so far, we've discussed how COVID started, how the variants developed, how there was a lot of lack of clarity to extreme clarity on what to do. And now there is amnesia, where we've forgotten that there was a disease called COVID. And this CME and this discussion is to remind us that the basics are the same. You treat your patient and their comorbidity like any other patient. Focus on a quick diagnosis, focus on close monitoring, focus on really looking at their oxygenation, as well as all the other secondary factors that get people better in an intensive care or in the ward. The other bit that we need to remember is that we still need to continue testing.

Vaccines still have a role. So if we were to wrap up what we've been talking about for the last 30, 40 minutes, and of course, thank you so much for your insight, Cristina. It's amazing to have someone with your experience share both the theory and the practice. And I know people in Italy are very pragmatic and I really appreciate the way, like you said, you guys were right after China, you had to handle the brunt, and I'm sure you've learned a lot just by doing the things there. So if we were to wrap up, what would be some final points from this activity? So I would think that some of them are, variants do not dictate treatment. I think it is important to apply the evidence-based standard of care across variants, according to the disease severity rather than what the lineage is. I have a couple more points. I would love to hear from you too. I think time is of the essence.

As providers, we need to follow our patients carefully and ensure early intervention is performed because that is the single biggest predictor of treatment outcomes. One of my teachers when I was in training used to say, do

bedside rounds, don't do doorstep rounds, meaning you get to the bedside of the patient, and especially if you're looking at a patient, see how they're breathing, look at the ventilator settings, look at the BiPAP settings, those are very important, and of course, reassure the patient. And I think it's important to treat the patient, not the variant. And while following the variant trends is important to see how it may impact our prevention and isolation protocols, more importantly, we focus on the patient-specific factors, just as in this case, age, comorbidity, and immune status when you are developing individualized treatment plans.

So I think these would be the key takeaways I am thinking of when I discuss this case and look at the current COVID scenario. And I also feel our surveillance can get more scientific. There may be better ways to look in the community to see and pick up the disease much earlier and almost use an influenza type surveillance mechanism, maybe something important that we should get back to. Love to hear from you, Cristina, what your thoughts are.

Cristina Mussini, MD:

I completely agree. I think that everybody want to erase the word COVID. I think that the COVID surveillance has joined the influenza surveillance in Italy and now is the respiratory disease surveillance. So we keep going with the surveillance, and this I think is very important. It's important to look at the variants as we are doing with the modification of the influenza virus. We also monitor the RSV virus. And the problem is that, as you said, we have to look at the patient because we can prevent this disease to become serious. If we treat with antivirus as soon as we know that this person is at risk of a bad evolution, and we have the weapons now, and it will be really stupid, I think, not to suggest vaccination for the fragile and not to use the antiviral when they acquire the infection.

Sai Praveen Haranath, MBBS, MPH, FCCP:

That makes sense. And if you were to ... Go ahead. There's some other themes that I can think of to summarize this. You've heard of the SMART goals? Do you think we can use, frame all of this into that?

Cristina Mussini, MD:

I think that you did a great summary, and I want to conclude our program today with our SMART goal, specific, measurable, achievable, relevant, and timely. This is what we hope that our audience will take from this presentation to apply to their practice, I have to say. So utilize guideline concordant protocols. So look at the evidence-based medicine and disease severity rather than specific variants when making inpatient SARS-CoV-2 treatment decision in at least 80% of patient over the next six to 12 months. Prioritize patient vulnerabilities over specific variants when selecting inpatient treatment plans in at least 80% of patient over the next six to 12 months, recognize the benefit of earlier versus delayed initiation of inpatient SARS-CoV-2 treatment, still in at least 80% of patient over the next six to 12 months.

Sai Praveen Haranath, MBBS, MPH, FCCP:

Perfect, so that's amazing. So it's been really fun. And really, thank you, Cristina, for engaging and sharing your wisdom with us. I would like to let our audience know that in order to receive credit for today's activity, you will need to complete the post-test and evaluation online. And I think the CMEO Snack is one of a four-part series, and we hope that you'll take advantage of all the short and focused activities in the series. These series and a

wide variety of activities and resources on infectious diseases are available on the CME Outfitters Infectious Diseases Hub for both healthcare providers and patients. I would love to thank the CME Outfitters team for helping make this program possible. And Vee, thank you so much for taking your time and participating. Christina, any closing remarks?

Cristina Mussini, MD:

Sai, it was a really, really great discussion, and I think that putting together people from different part of the world is really a winning strategy because we could exchange our clinical experience, our ideas, and I think that this is also very, very helpful for the audience.

