Guidelines-Based Therapeutics for Hospitalized Patients with SARS-CoV-2 Infections

CMEO Podcast Transcript

Jason D. Goldman, MD, MPH:

Hello and welcome. On behalf of CME Outfitters, I would like to welcome and thank you for joining us on the CMEO Snack: *Guidelines-Based Therapeutics for Hospitalized Patients with SARS-CoV-2 Infections.*

This CME 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 FDA. We'll also talk about any off-label uses, or off-guidelines uses if we discuss these during this Snack.

I'm Jason Goldman. I'm an infectious disease and organ transplant physician at Swedish Medical Center in Seattle, Washington, and on faculty at University of Washington and the Fred Hutch Cancer Center. I'm joined today by my distinguished colleague, Dr. Cristina Mussini.

Cristina Mussini, MD:

Yeah. I'm full professor of infectious diseases, and I'm the chief of the Department of Infectious Diseases at the University of Modena and Reggio Emilia in Modena, Italy.

Jason D. Goldman, MD, MPH:

Great. Thanks so much, Cristina. Today, we're going to be talking about how we're going to incorporate guidelines recommended SARS-CoV-2 therapies into the treatment of hospitalized patients to improve clinical outcomes and reduce mortality.

Cristina, from your perspective, when you're looking at the treatment landscape for COVID, what are some of the gaps in the current system that you see in terms of directed medical therapy for hospitalized patients?

Cristina Mussini, MD:

I think that somehow after the shock of the pandemic, doctors tried to forget, which are the good clinical practice in COVID, so there is an inconsistent patient stratification based on disease severity. And also, there is a limited oral antiviral awareness, so about eligibility, prescribing, benefits, and finally, a delayed application of immunomodulatory therapy.

Jason D. Goldman, MD, MPH:

Yeah, it's true. I think the pandemic severity has waned, but the disease is still there, and we're still seeing cases. So, to ground us in our strategies to tackle unique clinical scenarios and how and where to act, let's walk through a case scenario.

Cristina, can you tell us about the patient initials DR?

Cristina Mussini, MD:

Yeah, DR is a 60-year-old male with multiple myeloma undergoing maintenance treatment for five years with lenalidomide. Three days ago, he started feeling sick with cough, and at night developed low-grade fever with

the following vitals. I mean, it started with a low temperature, so 37.6 Celsius, 99.7 Fahrenheit. He had a little tachycardia with 89 heartbeats, and the blood pressure was in the normal range and as the respiratory rate, but this was three days ago.

Yesterday, the temperature increased, as did the heart rate, the blood pressure, and the respiratory rate with 22 breaths per minute. So, since he knew that the COVID was circulating, he decided to take a self-test for SARS-CoV-2 that turned out positive.

This morning, his situation really was worse. It worsened in experience, a shortened breath, so he was scared, and he came to emergency room, and his saturation or room air was 86%. In his clinical history, he had a COPD because he was a former smoker, but he smoked a lot.

And so what would be your first line management option?

Jason D. Goldman, MD, MPH:

Yeah, this is an interesting case. So, he's 60 years old, and he has multiple myeloma, he's on lenalidomide, so he's maybe a little bit immunosuppressed but not very immunosuppressed, but I don't know what treatments he's had in the past, so his net state of immunosuppression might be higher. I don't know about his frailty. And he has COPD, so I'm not even exactly sure how to contextualize that.

SpO2 of 86%. On the surface it seems very low, but that may or may not be close to his baseline. He might live at say 88%, 89% or something, so he might be just slightly off his baseline.

However, given that low oxygen sat and he's presenting to the ER, he has a number of potentially high-risk comorbidities. We're going to be admitting him to the hospital. And based on his symptoms' onset of approximately three days ago, I'm going to be thinking about antiviral therapy as a first line therapy, because of his hypoxia, and the fact this might be also partly explained by COPD exacerbation. I'm thinking about steroids as well.

Cristina Mussini, MD:

Yeah, I perfectly agree. And also, I think that his clinical stage is somehow in between severe and critical because actually, his room saturation is below 90%, but it doesn't need for now, in my experience, high flow nasal cannula, or non-invasive ventilation. What do you think?

Jason D. Goldman, MD, MPH:

That's a really good point, and I think we're probably going to put him on oxygen and see how he does. He may need escalating doses of oxygen as we see what happens and his clinical case evolves.

All right, well, let's see how we should tackle this type of a case based on the latest IDSA guidelines. That's the infectious disease side of America. I personally utilize these guidelines. Previously, I had used the National Institute of Health guidelines, but these have been sunset, so they're a little bit out of date compared to the IDSA guidelines. That's going to be how I'm going to ground the research basis for my decision-making.

Cristina, how would you classify DR's disease severity?

Cristina Mussini, MD:

Yeah, as I said, I agree with you that I would start with antiviral because the window from the onset of symptoms is the right one. It was just three days ago, so I think that that would be perfect.

On the other hand, considering the room saturation, it could be critical, but his general condition with all the other parameters seems like he's severe, because as I said, we don't need to have high flow nasal cannula, or non-invasive ventilation. So, what I would do, I would do exactly what I said. I would start with antiviral, and then go to also on steroids because he is doing oxygen.

And which antiviral would you prescribe?

Jason D. Goldman, MD, MPH:

Yeah, let's talk about the IDSA recommended and available antivirals. The first one for hospitalized patients will be remdesivir, it's a nucleoside analog that inhibits the RNA-dependent RNA polymerase, or RDRP. This has been studied in multiple randomized clinical trials that has shown efficacy, especially in mild to moderate disease for outpatients or moderate to severe disease for inpatients. That's in patients who are on oxygen, but are not mechanically ventilated. In that context, it's shown more inconsistent results.

We also have nirmatrelvir or ritonavir or paxlovid. This is a protease inhibitor combination that inhibits the 3CLpro, the main protease that blocks viral replication. Ritonavir is a pharmacologic booster that boosts the nirmatrelvir component by inhibiting CYP3A4 metabolism, and this is one factor that we're going to need to consider as we prescribe that. This has been clinically indicated and FDA approved for mild to moderate disease in adults and children who are greater than 12 years old and greater than 40 kilograms who are at high risk for progression to severe disease.

The last antiviral available to me here in the US is molnupiravir. This is a nucleoside analog and it inhibits also the RDRP, but it actually works as a mutagen to the virus, and it had a little bit less efficacy in the foundational registrational trials, and still not FDA approved in the United States. It's available under emergency use authorization, and it's indicated for mild to mild severe disease in adults who are at high risk for progression. So, that's what we have available here.

What about you, Cristina? What antivirals are available in your context in Italy?

Cristina Mussini, MD:

But actually, in Italy we follow EMA. So, the only one of these four have been approved by EMA are Remdesivir and nirmatrelvir-Ritonavir. While molnupiravir was not approved after the registrational trial, and we don't have ensitrelvir that I think that is used only in Japan and Singapore. So, I think that we would've to choose between Remdesivir or nirmatrelvir-ritonavir.

Jason D. Goldman, MD, MPH:

Yeah, interesting that you mentioned ensitrelvir, that's another protease inhibitor. It inhibits the 3CLpro, similar to the mechanism for nirmatrelvir, and that has some interesting data in prevention. So hopefully we'll get to see that agent soon here in the United States. But I agree that one's not available to me here at this time.

All right, well, what about the available immunomodulators? Can you tell me about those, Cristina and what you're going to use in your setting?

Cristina Mussini, MD:

So, the Dexamethasone is exactly what we said. When someone enters with COVID and he needs oxygen, we prescribe immediately the dexamethasone. But when there is the beginning of the so-called cytokine storm, it depends on which is your experience. For example, I published one of the first paper on tocilizumab in COVID, and so I mean, I am not only affectionate, but I think that it's a great drug.

So, probably my choice will be on tocilizumab, even if for example, in our intensive care unit they like baricitinib. And which is your experience?

Jason D. Goldman, MD, MPH:

Yeah, similar to you with tocilizumab, I've been involved in some of the development for baricitinib, so that has been my practice pattern. Initially, we were using a lot of tocilizumab in the very earliest parts of the pandemic, but then we learned it didn't work. Then some further trials came out from recovery and others remap cap that showed tocilizumab work. So, I think of both baricitinib and tocilizumab as two great first-line options for further immunomodulatory blocking.

When patients are progressing past the need for low-flow oxygen and when they're getting into that non-invasive ventilation with BiPAP, or high-flow nasal cannula, that's when I'm thinking about tocilizumab or baricitinib. tocilizumab, of course, is a IL-VI receptor inhibitor, and baricitinib is a JAK-I and JAK-II inhibitor. So, they fundamentally block different inflammatory pathways, but both have been proven effective, and baricitinib is actually FDA approved for the of COVID in the United States.

So, I think of them very similarly. And one feature is I really haven't seen the need for these in so many cases in recent months. How about you Cristina? Have you seen any kind of worsening that's required immunomodulation beyond dexamethasone?

Cristina Mussini, MD:

No, no. I have to say not. What I wanted also to say is that we have also some markers like CRP above 7.5 that can help us in prescribing these drugs. I think that during the Omicron era, even if the cases are there, because sometime, in most cases, COVID is like the cherry on the top of someone who has comorbidities or older age, we don't see the classical clinical evolution that we were used to see during the first waves of the pandemic.

Jason D. Goldman, MD, MPH:

Yeah. And Cristina, I know the IDSA recommendations have a few alternative immunomodulatory therapies that we can choose from. Do you want to tell us about what else is available?

Cristina Mussini, MD:

Yeah, I would start with anakinra because anakinra was the first one. It is a recombinant IL-I receptor antagonist, and it was the first one where the trial, even if you have to have markers that are not widely available to use

anakinra. And other one are infliximab, that is a TNF-alpha inhibitor. But I have absolutely no experience with infliximab in these patients.

You see that the indication are the same for all of them. And the last one is abatacept, that is a T-cell stimulation modulator. It blocks T-cell activation, and it's still to be prescribed in severe or critical SARS-CoV-2 when other agents are available. I mean, I think that these are really alternative, as you said, and the one that at least in Italy has been used more frequently during the pandemic was an anakinra. I don't know if in the US there has been some experience with Infliximab or abatacept.

Jason D. Goldman, MD, MPH:

Yeah, I know that the initial trials for these came in a little bit late but showed positive results. I also don't have experience prescribing these drugs in severe or critical SARS-CoV-2 infection. And I would reach for them if other agents are unavailable. At one point, in the pandemic, we did have a tocilizumab shortage and that's when a lot more baricitinib was prescribed, but I wouldn't hesitate to reach for these if I felt they were indicated when tocilizumab or baricitinib are unavailable.

All right, well, let's get back to our case now. Cristina, given all these recommendations from the IDSA, how would you approach this patient in your practice setting?

Cristina Mussini, MD:

I think that as we said, we have to assess how it's progressing, the disease, so we have to monitor the patient. This is something that is very important. We have learned it from the early days of the pandemic that this infection could really progress rapidly.

So, we have to monitor them and not just in emergency room, we have to do a severity classification, and we have to start antiviral therapy since it is between five, seven days from the beginning of the symptoms. This patient is perfect because it was three days, and then use corticosteroids because he really needs oxygen, even if not high-flow. But he has 86% saturation in room air. So, he needs Dexamethasone, six milligram daily. And also, we use anticoagulant test prophylaxis with the low molecular weight heparin for all hospitalized patient.

And do you do the same?

Jason D. Goldman, MD, MPH:

Yeah, I think that really captures the standard approach as recommended by guidelines such as IDSA. I think it'd be interesting to see how this case progresses. We didn't talk about whether this patient was vaccinated in the past, if he's had prior SARS-CoV-2 infections in the past. My experience in the current era with the recent circulating variants is that disease severity has really gotten a lot less severe. So, I think that probably when we look up all that information, this patient probably has had vaccination in the past, hopefully, more recently than not, and he's been keeping up given his high-risk comorbidities like COPD especially.

But he's probably also had at least one or more SARS-CoV-2 infections. And these things are going to also modulate the severity, and he'll probably do fine on supportive care with oxygen, antiviral therapy with remdesivir, and immunomodulation with dexamethasone for the hypoxia and the COPD exacerbation. But if he progressed and was needing a more high-flow nasal cannula or CPAP, I would be reaching for some of those

other immunomodulators like tocilizumab or baricitinib. And then if he progressed again, I would be thinking of continuing the therapeutic anticoagulation for VTA or high-risk patients.

Cristina Mussini, MD:

Yeah, I agree because I think that for sure, Omicron is less aggressive than alpha or delta variants. So, there is this, but we actually don't know how would be the severity of the picture if the patient never vaccinated, never experienced COVID, never took antiviral. So, it's something that is a mix of these protective things that will prevent him to go to intubation, for example. So, I think that this is very important.

And you see in monitoring and escalation it's said inflammatory markers to monitor daily inflammatory markers. I would say only CRP because I don't know your experience with IL-VI, but IL-VI is extremely variable and erratic. So, which is your experience with IL-VI?

Jason D. Goldman, MD, MPH:

Yeah, my experience has been a little bit hot and cold. We were giving it a lot during the beginning of the pandemic. We stopped giving it for a while when the off-label therapies really fill out a favor except for clinical trials. And then we started giving it again once clinical trials showed efficacy. I can say I can recall some patients that made miraculous recoveries with Tocilizumab, and I've also seen some patients where it seemed like it didn't do anything, but I think I rely more on the data rather than my personal anecdotes. And I think that both of these therapies, tocilizumab and baricinib, have good efficacy if he should progress.

And I think you made a really important point too about the vaccination. The people who are winding up in the hospital these days really do seem like those who have never been vaccinated and those who are on immunosuppression for various reasons.

And the more sort of moderate to severe cases like patients with active hematologic malignancies or a history of a hematopoietic stem cell transplant or an organ transplant, or other patients who are on anti-B cell therapies seem the most at risk for hospitalization and more severe outcomes. And these are the patients that I'm really focusing on antiviral therapy. Sometimes even beyond that initial window of five to seven days, I'll give antiviral therapy if I think that we could prevent a persistent infection, or other sequela like long COVID, for instance. And these are more off-label indications for antiviral therapy, but I think there's a very reasonable evidence base with what's been seen with SARS-CoV-2 persistence in immunocompromised persons to prescribe it outside of that initial five to seven-day window.

How about you, Cristina? Are you giving antivirals similarly for immunocompromised persons?

Cristina Mussini, MD:

Yeah, absolutely. Also, because... I mean, while we know that in SARS-CoV-2 infection we have these two phases, the viral phase and the inflammatory phase, it is true that in immune compromise, the viral phase never ends. So, they continue to have a replication of the virus. And I think so that in patients severely immunocompromised, we should not rely strictly on this window.

Another thing that is very important is that... I mean, in this period, for example, there's a very relevant circulation of bacteria, pneumonia-like mycoplasma, or like pneumococcus, and it's important to exclude them. I

mean, it could be not only COVID, and also, to exclude if there is a sudden deterioration of the respiratory function to exclude the pulmonary embolism. I think that these things should be kept in mind.

Jason D. Goldman, MD, MPH:

Yeah, those are great points, Cristina. Thanks for raising those. All right, so let's go through the framework for inpatient treatments from the IDSA guidelines. It's broken down by disease severity. We have mild to moderate, severe, not critical, critical, not mechanically ventilated, and critical with invasive mechanical ventilation.

For each category, there are first line and alternative treatments. In the mild to moderate category, the first line treatment recommended is nirmatrelvir-ritonavir. This is predominantly for outpatients, and because of some of the CYP3A4 drug-drug interactions, this can be challenging to give in the inpatient setting, where if someone is admitted but has mild to moderate disease without hypoxia, Remdesivir might be a good choice in that setting. It's listed by the IDSA guidelines as an alternative option, and as we mentioned, molnupiravir. There might be some very rare uses for convalescent plasma, it was listed there. There's also some high-titer convalescent plasmas in studies still, but aren't readily available.

For severe or non-critical cases, that's where we have the hypoxia evident or an SpO2 of less than 94% of room air or needing low-flow nasal cannula supplemental oxygen. That's where we're reaching for Dexamethasone plus Remdesivir if we're in that early viral period as first line treatments. Alternative options can be other steroid forms or adding other immunomodulators, as we've discussed. For critical cases that are requiring noninvasive oxygenation support, we're reaching for Dexamethasone and Tocilizumab as first line therapies and using baricitinib or other alternatives as second-line therapies.

And for those with critical illness requiring invasive mechanical ventilation, dexamethasone and Tocilizumab are the first line therapies for baricitinib as an alternative therapy. The IDSA recommendation does recommend avoiding the use of remdesivir for those who are on invasive mechanical ventilation to start. But again, as an infectious disease doctor, I might be contextualizing that recommendation in the context of my patient. If it's very early in their disease course and that's clear from their symptoms' onset, or if they're immunosuppressed, I might utilize an antiviral in that setting as well.

Cristina, I know there's some significant differences in the overall patient approach relative to the region of the world in which clinicians may practice. Based on your experience in Italy, can you discuss any unique regional variations to inpatient management for patients who are admitted with COVID-19?

Cristina Mussini, MD:

I have to say that in Italy, the only difference could be the different choice. If someone prefer to prescribe tocilizumab or baricitinib as in the inflammatory phase, and as I said, we don't have molnupiravir, or we don't have convalescent plasma because after the results of the recovery... In theory, it should have an antiviral effect, but the EMA decided not to allow the prescription of this.

So, I think that these are the only difference, but let's think that we have been facing a pandemic in the last five years, and the regional differences really are also with low and middle income countries where it has been impossible to prescribe immunomodulatory agents for their price. So, I think that the real difference is about the high cost of antiviral and of immunomodulatory agents. While prednisone was widely available, I have to say that luckily in low and middle income countries, the population is much younger than in my country at least, and

probably less obese. So they needed less. They had a very low mortality. So, talking about this, the characteristic of the population prevent the same mortality that we had in our countries despite not having access to the more expensive drugs.

Jason D. Goldman, MD, MPH:

Great. And I know there are some other organizations providing guidelines for different parts of the world. For instance, the WHO, of course, has guidelines, the NICE guidelines in the UK, and the National Health Commission in China may guide slightly differing strategies in those regions.

Cristina Mussini, MD:

Yeah. Also, for example, in UK, it depends on the NICE, right? The guidelines on the basis of the deal on the price of different drugs. This is true for HIV. It is also true for COVID. It depends on the market deal they could obtain with the different companies. So, that's why, for example, in Italy, we follow the IDSA because we know that in UK they are using a different approach.

Jason D. Goldman, MD, MPH:

Yeah. And the WHO guidelines interestingly don't give as much support for antiviral use, for instance, for Remdesivir, even though the final analysis of the solidarity trial did show a small mortality benefit there. So that's interesting to note.

All right. Well, Cristina, thank you so much for highlighting some of these regional differences. Let's wrap up our discussion with some final points to take away from this activity.

Patient stratification by disease severity is the first and most critical step. Corticosteroids remain the cornerstone of therapy for hospitalized patients requiring oxygen. And the choice of antivirals and potential immunomodulators depends on patient-specific factors. So, you should be aware of your primary national guidelines and understand key differences in international recommendations.

Cristina Mussini, MD:

So, let's put the information into action. So, which are the takeaways from this program that you can implement in your clinical practice to improve patient care? So, we focus on early initiation of guideline-recommended corticosteroids the same day for inpatients requiring oxygen. We have underlined this many times. Implement initiation of antiviral therapy and potential immunomodulatory therapy among eligible encounters.

And finally, ensure implementation of severity-based care pathways to initiate early supportive management for eligible SARS-CoV-2 patients.

Jason D. Goldman, MD, MPH:

Thanks, Cristina. I'd like to let our audience know that in order to receive credit for today's activity, you'll need to complete the post-test and evaluation online. This CMEO Snack is one of a four-part series. We hope that you'll take advantage of all the other parts of the program, and these short and focused activities in the series.

These activities and a wide variety of activities and resources on infectious diseases are available on the CME Outfitters Infectious Disease Hub for both healthcare providers and patients. We want to thank CME Outfitters for helping make this program possible, and we thank you so much for participating.

Cristina Mussini, MD:

Thank you very much. Also, thank you very much for your attention.

