Early Diagnosis and Timely Treatment in SARS-CoV-2 Infections

CMEO Podcast Transcript

Jason D. Goldman, MD, MPH:

Hello and welcome. On behalf of CME Outfitters, I'd like to welcome and thank you for joining us today on this CMEO Snack, *Early Diagnosis and Timely Treatment in SARS-CoV-2 Infections*. This CMEO Snack is supported by an independent educational grant, Gilead Sciences. This activity may include discussions of products or devices that are not currently labeled for use by the US FDA. When we do speak about off-label or off-guidelines uses, we'll call that out. My name is Dr. Jason Goldman. I'm an infectious disease and organ transplant clinician at Providence Swedish Medical Center in Seattle, Washington. I'm also a clinical associate professor in the division of Allergy Infectious Diseases at the University of Washington and an affiliate investigator at Fred Hutch in Seattle. I'm joined today by my distinguished colleague, Dr. Cristina Mussini.

Cristina Mussini, MD:

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

Jason D. Goldman, MD, MPH:

Thanks, Cristina. To frame the discussion today, let me review our learning objective, which is to apply evidence-based strategies for early diagnosis and timely initiation of appropriate SARS-CoV-2 therapies to optimize patient outcomes. To get us started, let's take a look at the case of KP and examine how our approach to the onset of COVID in the early stages in appropriate therapeutic management. All right, our patient is KP, who's a 52-year-old female with relapsing remitting multiple sclerosis, who's undergoing maintenance treatment for seven years on ocrelizumab, which is a B-cell depleting therapy. On day zero with her symptoms onset, she reported fever, malaise and mild cough that started about five days ago. Initially thought to be a viral bronchitis by her primary care physician. She last received a SARS-CoV-2 booster approximately two years ago. And now presents to the ER with pleuritic chest pain and dyspnea. The vital signs in the emergency department included a temperature of 38.3 degrees Centigrade, which is a 100.9 degrees Fahrenheit, tachycardia with a heart rate to 110 beats per minute.

Normal blood pressure and a respiratory rate that was elevated at 30 breaths per minute with a slightly low oxygen saturation of 93% on room error. Diagnostics performed in the ER included a CT angiogram which showed bilateral segmental pulmonary emboli and a SARS-CoV-2 NAT test, which was positive. In terms of management, she was started on therapeutic rivaroxaban for anticoagulation and admitted for monitoring and further management. On hospital day two, her respiratory status worsened with cough and mild hypoxia, and labs that were trending include a rising CRP and worsening lymphopenia. The vital signs on hospital day two included low-grade temperature elevation with a T-max of 38.2 degrees centigrade, ongoing tachycardia with a heart rate of 108 beats per minute, still slightly elevated or normalized blood pressure and a respiratory rate of 28 breaths per minute. But the oxygen saturation was decreasing with an SpO2 of 90% on two liters of nasal cannula. She continued on the anti-coagulation for the pulmonary embolisms and had ongoing monitoring for drug-drug interactions, bleeding wrists, and VTE progression. So infectious disease was consulted. Cristina, what would be your next course of action?

Cristina Mussini, MD:

Yeah, she has been already diagnosed with COVID, so we have to understand what will be the evolution of this situation. One thing that I found really strange is that being an immune depress, she received the last SARS-CoV-2 booster two years ago. This is very, very strange to me, because I'm not sure, and I will ask you if the treating physician usually suggests to do the vaccination in this patient. And if they have a personalized access to the vaccine, do you have it in the US?

Jason D. Goldman, MD, MPH:

Yeah, I agree. Cristina, I think there are a number of potential misses in this case. As you mentioned, she's immunocompromised. She's on an anti-B cell therapy, which is going to leave her antiviral immune responses to be severely impaired. And I agree, she should be getting vaccinated at least annually. And according to the CDC recommendations for a patient with this degree of immunosuppression, twice annually. It's also noteworthy to think about other potential preventatives that could have been applied in her case. We have the pemivibart, which is a long-acting monoclonal antibody that can be given to augment the prevention of SARS-CoV-2 in patients who might not mount an appropriate response to SARS-CoV vaccination, which would be exactly indicated in her case, given the B-cell depleting therapy.

Cristina Mussini, MD:

But now that she has this severe COVID, I would say since she's an immune compromise, so the two phases of the COVID-19, one that is the first one that is viral phase. And the second one that is inflammation phase, inflammatory phase are not so separated. Because there is a long-lasting viral replication that is never controlled by the immune system of the patient. So I would prescribe in this patient for sure, antiviral. And the other problem is that sometimes you need to make her maybe becoming negative earlier because she has to undergo chemotherapy. So I think that the antiviral in these patients is very important independently from the stage. And then obviously the exometasone because she has 90% in two liters. So I think that this would be very important. Would you do differently?

Jason D. Goldman, MD, MPH:

Exactly. And thanks for highlighting. That's another gap. And the failure to prescribe the antiviral therapy and even diagnose the infection when she first presented to care in someone who's high risk, like she is based on her immunosuppression. When I think about the patients I see admitted to the hospital, it's often a result of some gaps that are delaying effective treatment. And I think of three main types of gaps about why patients miss the window for effective treatment. Because remember, the antiviral therapies are going to work best when applied early. And we're already into the late part of that early phase of her disease process where she's at the end of the replication window where the virus is replicating the greatest and we're starting to see some more systemic inflammation effects that are causing her hypoxia. So the three main gaps that we tend to see now are clinician gaps, patient gaps and access gaps.

From clinician gaps, there might be a difficulty in rapidly identifying high-risk patients or keeping up-to-date on evolving therapeutic guidelines. Or just potentially wanting to forget about the pandemic that changed all of our lives so much. This has occurred and I see it regularly in my practice. I think we saw that in this case the PCP thought it was a bronchitis flare. We also see patient gaps, and this might be on the patient side, a lack of awareness of personal risk factors. In her case, the immunosuppression might've contributed why she hasn't kept up on her vaccinations, for instance. And there's also a tendency in some patients to delay a seeking care

for what some might consider mild symptoms, and then there's access gaps. That's where disparities in access to testing or healthcare facilities or therapeutics might limit certain people based on their geographies or other logistical or demographic barriers. Any other thoughts on that, Cristina? What are you seeing in your care setting?

Cristina Mussini, MD:

No, I agree. Because what we said is that doctors are tired of COVID, but also patients are tired of COVID. So this delay in seeking care for mild symptoms could be bidirectional. It could be a primary care physician who said you are immune suppressed, but not so much. Maybe it doesn't know exactly that she didn't vaccinate for the last two years. And maybe she said, "Oh, I'm feeling fine." They tend to forget how severe could be the disease in people who are immune compromised. So I agree with you and I think that we have in a way to reinforce this idea that COVID has not disappeared, probably without a shift, an antigenic shift, it'll not be a severe problem as it was. But it is still there and we have to live with it. Absolutely. And so people who are immune suppressed has to be made really, really aware that they are at higher risk of hospital admission and maybe of severe disease.

Jason D. Goldman, MD, MPH:

Yeah. Thanks for those thoughts, Cristina. I also like to think about none of the currently available antiviral therapies are extremely easy to prescribe, and we'll get into that a little bit later with what might be some of the challenges with the available options. But first, let's look at the early signs and symptoms that should raise suspicion for COVID-19. When patients are presenting to healthcare or when they are monitoring their own symptoms at home, before deciding to test or present to healthcare. Of course the respiratory symptoms, a cough, shortness of breath, sore throat, URI symptoms and chest pain can all be indicative. We have gastrointestinal symptoms, nausea, vomiting, diarrhea, abdominal pain, and sometimes loss of appetite. And then of course, general systemic symptoms that can be present with other viral infections too. We see fevers and chills, fatigue, muscle soreness, headaches. And what might be more specific to SARS-CoV-2 is the loss of taste or smell.

Cristina Mussini, MD:

And also, if I can say, I think that the problem is that now while COVID could be in every month of the year, now there is flu together with COVID. And so I think that people many times we will talk about the testing, but many cases they don't have the swab, the test at home. So this contributes to the delay, I think. The fact that they think, well, maybe it's a flu, they don't want to think about COVID unless they have this very classical sign of loss, of taste or smell that is really, really COVID associated since the first wave.

Jason D. Goldman, MD, MPH:

Yeah, I agree. So on top of recognizing the early signs of COVID, it's important to understand the different phases of the initial SARS-CoV-2 infection that tend to influence which therapeutic options we choose. Cristina, can you go over the phases of COVID infection and see how they're presenting clinically in your patients?

Cristina Mussini, MD:

Yeah, we have the first phase, as I said, that is a viral phase where we have a high viral load, especially in upper respiratory tract, that this is what makes the difference with, for example, SARS-CoV-1, that was a more self-limited epidemic while having this replication in the upper respiratory tract makes this virus very, very easy to spread. We know that at the beginning could be asymptomatic. Or could have mild symptoms like fever, cough,

fatigue, body aches, very similar to a flu. And this phase lasts five to seven days from symptom onset. And this should be the perfect window for antiviral immunocompetent or slightly immunocompromised, I would say. Because in severe immunocompromised we said that this window could be prolonged. And then it's followed by lower respiratory tract involvement that was really scary at that time with pneumonia, ground glass opacities, dyspnea, increase in dyspnea, worsening dyspnea with severe hypoxemia, that is the pulmonary phase. And so 5 to 12 days from symptom onset.

And then the inflammatory phase that is characterized by the cytokine storm with the increase in all pro-inflammatory cytokines, IL-6, IL-1 BTNF alpha. And these are also the target. These three cytokines are the target of the drugs like tocilizumab for IL-6, IL-1, TNF-alpha, we have seen infliximab, and then an increase in CRP and D-dimer. Obviously the complication are acute respiratory distress syndrome, septic shock, multi-organ dysfunction. These patients, if they don't respond to anti-inflammatory agents, immunomodulatory agents, they end up in intensive care. And this systemic inflammatory phase could onset two, three weeks from symptom onset.

Jason D. Goldman, MD, MPH:

Great. Thanks for that overview of the phases of SARS-CoV-2 infection. Next I'm going to talk briefly about SARS-CoV-2 diagnostic assessment tools. We have basically two main types of tests. Of course, we have molecular tests, PCR or NAAT, nucleic acid amplification tests, and rapid antigen tests. The PCR tests or the NAAT tests are usually in center tests, whereas the rapid engine tests can be done at home. The PCR test is really the gold standard. It has very high sensitivity and specificity.

So for diagnosis in the acute phase of illness, this is the gold standard. And it can detect infection sometimes even one to two days before the symptoms onset, given its high sensitivity. The limitations of course to PCR testing, it's in center only longer turnaround times, higher costs. Whereas the NAAT tests with slightly lower sensitivity benefit from being widely available in the community. They have a quick turnaround time, approximately 15 minutes, they're available at the point of care for patients to do in their own homes. And they're cost-effective. But there's some different performance issues, which we can talk about with the rapid antigen tests. How do you utilize SARS-CoV-2 tests in your setting, Cristina?

Cristina Mussini, MD:

Yeah, at the hospital we have RT-PCR. And so we use it especially in emergency room. They do RT-PCR for SARS-CoV-2, but they also test for other respiratory viruses, like flu or in some centers like metapneumovirus or RSV. While at home use a rapid antigen test. But as I said before, is it's very rare that people have these tests at home now. So I am pretty sure that there's a lot of COVID that circulates because there's a lot of diagnoses that are not done because they don't test. I don't know, what is your opinion?

Jason D. Goldman, MD, MPH:

Yeah, I've also noticed that I think in our setting in the United States and in Washington state in particular, we had free home tests available for a long time. So I think many people got ahold of some of these kits. And I'm still seeing quite a bit of patients coming into clinics for the hospitals saying that they tested positive on a home rapid antigen test. So yeah, I'm definitely still seeing that. Interestingly, this year we have for the first time available a dual test for both a SARS-CoV-2 and influenza that are available in the rapid engine test format. So that's I think quite a good tool because these are the two respiratory viral diseases which we have antiviral treatments for. So these are really good tools for patients to use in their setting when they have some of those

early signs of SARS-CoV-2 or other respiratory illnesses to rule out the treatable causes. And especially important for patients who are living with immunosuppression.

Cristina Mussini, MD:

Yeah, I completely agree. I think that for people who are not immunosuppressed and the symptoms are similar to a cold or a non-severe flu, influenza, it's not so important, but for epidemiological purposes to test. But because they will never take an antiviral. While for immune suppress having a rapid diagnosis that starts with the suspicious of being infected with SARS-CoV-2 is crucial because they can take advantage of antiviral treatment.

Jason D. Goldman, MD, MPH:

I couldn't agree more. And I think for those who are low risk, testing might not be as important because we don't have those treatment options. But it certainly still remains important for those who are going to go on to have the opportunity to receive antiviral treatment, which might bend the disease course. And we're certainly seeing that in our own health systems data, much fewer lab confirmed cases, I think because patients are using those rapid home tests and clinicians are charting those diagnoses.

So Cristina, after we've discussed testing, let's consider the clinical course of COVID and how it progresses. I'm going to quickly review the severity thresholds from the IDSA guidelines. And we have mild to moderate COVID, that's where the oxygenation is maintained without the need for supplemental oxygen. We have severe, non-critical COVID which is where the SpO2 dips below 94% of room error or the patient requires a low flow supportive oxygen. Critical COVID is defined as hypoxic. Now with SpO2, less than 90% of room air or the need for non-invasive support such as high flow nasal cannula or non-invasive ventilations like BIPAP, and critical COVID is where there's severe hypoxia and/or ARDS that requires invasive mechanical ventilation.

Cristina Mussini, MD:

So after considering the stages, we have to think that as we said that the beginning we would like to use antiviral not only during, as we said maybe is off label, but not only during the window that is in label, but being immune suppressed even we can prolong a little bit this period. And when we have the therapeutic option, we see that we have three antivirals in the states. So these are the treatment options. Nirmatrelvir, ritonavir, remdesivir, remdesivir. Our patient has been hospitalized, so the only option that we have is remdesivir that has to be used within five to seven days from symptom onset. And she has a low flow oxygen and the dosing is 200 milligrams per day on day one, then 100 milligrams daily for five days.

If she was only an outpatient, we could have also in the states two other options that are oral and one is nirmatrelvir, ritonavir in the same window as remdesivir five to seven days. And molnupiravir only where is available, especially if the other two are not available. I said only when it is available because for example in Europe it's not available, while in the states is an alternative option only if nirmatrelvir, ritonavir and remdesivir are not available. When we have to think about which of these options we could do, we have to evaluate the patient. So based on our case, what do you think, Jason?

Jason D. Goldman, MD, MPH:

Yeah, I think in the United States we'd approach this very similarly to what you just described, Cristina. In the FDA indications for these antivirals, they actually don't list the time criteria, but our guidelines such as the IDSA and the NIH before it's sunset, did list some optimal windows for initiating antiviral therapies. And many health

systems are also implementing their own formulary restrictions around these medications to try to utilize these therapies when they might have the most benefit. So that's where we get these optimal time windows from. A combination of the interpretation of the registration or foundational trials for the antivirals being interpreted by the guidelines. And then also health systems or other formularies, I'm restricting them to those windows. Of course, for certain patients like ours who are immunosuppressed, I might not rely on those windows quite as strictly based on what we've already discussed, that there might be prolonged replication, even those that's outside of the guidelines recommended optimal windows.

I would still apply antiviral therapy in this case. Since she's hospitalized, I'd reached first for remdesivir. As you've described nirmatrelvir, ritonavir is really mostly used for the outpatient cases. And I think that this could have been a good option that was missed in this patient's case. nirmatrelvir, ritonavir might've actually prevented hospitalization if it was given early in the course when she first presented to care with the primary care provider. If she had been tested and treated at that time, we might not be looking at a hospitalization and the need for advancing therapies. I think it's important to think about what might be some of the limitations to these various agents.

We didn't really hear in this clinical stem what other medications this patient's on, but because of the CYP3A4 interactions that the ritonavir component of paxlovid has. There may be some problems with administering that therapy. Had the infection been diagnosed. I've seen lots of immunocompromised patients who don't have any oral options because of the drug-drug interactions of the nirmatrelvir, ritonavir combination or the unavailability of molnupiravir or concerns about this antiviral therapy. What do you think about the drug-drug interactions of nirmatrelvir, ritonavir, Cristina?

Cristina Mussini, MD:

I'm a person who has been working with HIV since the beginning of her career and one tool that is very, very useful for us is the Liverpool website that likely during the pandemic was updated with the COVID session. So what we do, we check online for the drug-drug interaction on this site that you can see in the slide, that is very easy because you have to put just the name to click on the name of the COVID drugs or the other medication that the patient is on, and see if it turns red. That means that there's a drug-drug interaction that says that to avoid the medication. Or it could be green, that is a green light to use it. For example, this patient was on this drug, there was ocrelizumab. And actually, if she was given nirmatrelvir, ritonavir, it would be possible.

You see that no interaction expected. But then after she was admitted, she had this pulmonary embolism and so she was put on rivaroxaban at this point. nirmatrelvir, ritonavir versus rivaroxaban, you see it's red and it says do co-administrate. So I think that it's very important, especially in this patients who are very immune compromised. And who have several medication because this woman had only the drug for multiple sclerosis. But in general we have older patient who are on several medication. And it's important to check for all of them because ritonavir has drug-drug interaction with almost everything and it's important to have a look about this.

Jason D. Goldman, MD, MPH:

Yeah, I'd also add too, some of the really common drug-drug interactions with CYP3A4 and the ritonavir component include some of the antihypertensives like calcium channel blockers and also statin medications. These are meds that many patients are on who are elderly or have various comorbidities. But a really important one is with the calcineurin inhibitors like tacrolimus, a lot of my patients who've had organ transplant are on tacrolimus. And starting and stopping tacrolimus can really be very complicated for the clinical care teams and

the patients coordinate and be a risk for organ rejection. So many patients with organ transplant who get COVID-19 don't really have that as an option, which leaves molnupiravir and remdesivir as other options. Remdesivir of course, the main drawback is its need for IV infusion and in my setting, IV infusion capacity is limited.

We don't have a specialized center for SARS-CoV-2 infusions. So I actually prescribe molnupiravir with some regularity or at least offer it to patients who are presenting with COVID-19 after organ transplant. But these are some of the drawbacks to the currently available agents. Some of our other agents like obeldesivir that was tested did not meet the pre-specified efficacy outcomes. So that would've been an antiviral strategy, which would have minimal drug-drug interactions and likely be similar to remdesivir. But the clinical trials for that did not pan out.

Cristina Mussini, MD:

No, no. I completely agree that ritonavir is a nightmare for transplant patients and I don't know your experience, but transplant patient who underwent transplant did not have a very severe COVID. The worst one would be hematological cancer, but transplant for example, liver transplant, I don't know if they paid more attention in not acquiring during the really bad waves, I would say. But we didn't see very severe cases of COVID-19 in transplant patient, which is your experience.

Jason D. Goldman, MD, MPH:

Yeah, we've seen our fair share of bad outcomes unfortunately in patients with solid organ transplants. I think the literature also suggests lung transplant is likely to have worse outcomes, but anyone who's immunosuppressed after an organ transplant can have some certain bad outcomes. And that does seem to be higher than the general population even adjusting for comorbidities.

Cristina Mussini, MD:

Yes, yes. But it is just like HIV. There's this literature that is not so consistent. And it's really bad. Because for example, we have a big liver transplant center and kidney transplant, but we don't have lung transplant. So this could be obviously for lung transplant should have been something terrible with COVID-19. But let's go back to our case. And we are thinking about, she has a high CRP, she's already in the inflammatory phase. She's starting the inflammatory phase. So what do we have, which is our armamentarium during the inflammatory phase. First since she required oxygen, we need dexamethasone. And this is six milligram daily per 10 days or until discharge. And this, I have to say that has been, it's something that we are still feeling guilty about. Because at the beginning the Chinese said that the dexamethasone was contraindicated. So we didn't use dexamethasone.

You have to think that Italy was the second country that was hit by the pandemic after China. So we could rely only on Chinese data that showed that the mortality was very, very low, 4% in hospital mortality. While our hospital mortality was terrible. So we have really to recategorize everything. And among this it was that we didn't use dexamethasone until the recovery trial. The UK trial showed that it was fine to treat... Not only fine, but it was important to use it. Was this your experience or when you saw the patient you already had the data recovery.

Jason D. Goldman, MD, MPH:

Yeah, I think definitely recovery changed our view on dexamethasone and this really became the standard of care after that trial was published.

Cristina Mussini, MD:

And then if the inflammatory phase progress, we have this option that could be baricitinib or tocilizumab. These are the two recommended also by FDA and EMA. So it's in the way to interrupt the loop of the cytokine storm. And it's for patient who are progressing so severe, becoming critical. And for example, for tocilizumab, we have to monitor the CRP. Because when the CRP is above 7.5, we have to think about prescribing it. And together with this, we have seen that this patient had already the complication of pulmonary embolism, but we have to use as prophylactic agent. We have to do a prophylaxis for this that is low molecular weight heparin within 24 hours of hospital admission. And this is what we do. Do you do something different.

Jason D. Goldman, MD, MPH:

Yeah, I am doing something similar for stratifying patients for the more advanced immunomodulatory medicines like baricitinib and tocilizumab, I don't tend to rely on any specific CRP cutoffs. I tend to utilize a little bit more of the need for advancing oxygen support, like the transition from low flow to high flow nasal cannula, for instance. I found to be a good marker for applying these more advanced immunomodulatory medicines. Thankfully we haven't seen the need for too much use of tocilizumab or baricitinib recently. Many patients are getting admitted, they're becoming hypoxic, they're getting on antiviral therapy with remdesivir, getting on immunomodulatory therapy with dexamethasone, they tend to stabilize and start to improve from there. And this may relate back to the immunity status of people with prior vaccinations, sometimes multiple boosters prior SARS-CoV-2 infections or multiple reinfections. And the variants these days seem to be less pathogenic. So thankfully haven't really seen the need for more of these advanced anti-inflammatory agents. Yeah, but very similar approach.

Cristina Mussini, MD:

And also the problem is that, as you said, we have really to evaluate the stage of the disease and evaluate the risk-based stratification. There are several scoring tool. In the emergency room in our hospital they use the news and we do it also in our department. But as you said, after five years of pandemic, we don't really have to put the numbers in these tools, we know when the patient is progressing, what do you think? Are you using these tools?

Jason D. Goldman, MD, MPH:

Yeah, that's right. You kind of know it when you see it. And I also don't use these tools clinically. I know these and they're very useful for stratifying disease severity in research studies. I've actually also worked with another one that pneumonia severity index is actually useful. We created a skinny PSI that actually has components only available in EHR. But to really utilize these in real time, it takes additional effort on the clinician's part. And it might not improve from some of that disease stratification based on the IDSA guidelines for an individual case. But if some of these scoring systems can be incorporated into EHRs like the news or a skinny PSI for instance, these might help clinicians to better stratify patients. All right, Cristina, I'm glad we had this opportunity to discuss some of the similarities and also differences in regional approaches to risk stratification and management of COVID-19.

Let's highlight some of the key takeaways from our discussion today. First, early algorithm driven testing can yield results quickly enough to preserve the therapeutic window for timely treatment decisions. We talked about how to utilize rapid antigen tests there. Second severity and high risk stratification represents the pivotal first steps to direct patients onto the appropriate therapeutic management strategies. Corticosteroids, of course

remains foundational therapy and early antivirals. And in certain select situations, more advanced immunomodulatory therapies may be useful. And of course we want to align our care with national and local guidance, and label indications and combined with ongoing reassessment and these strategies can support optimized outcomes of SARS-CoV-2 infection.

Cristina Mussini, MD:

Yeah, so let's put information into action. So which are the takeaways from this program? Implement a rapid diagnostic pathway so that suspected SARS-CoV-2 inpatients received testing and are documented the results to enable early treatment decision. And I would say that in inpatient RT-PCR probably is the best. Ensure timely initiation or guideline concordant therapy for eligible patient within the recommended window. And we talk a lot about the treatment.

Jason D. Goldman, MD, MPH:

Thanks so much Cristina. And thank you all for your attention to listening to this CME activity. 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 of the short and focused activities in this series.

Cristina Mussini, MD:

I really thank you Jason for this helpful discussion and I thank you all for the attention.

Jason D. Goldman, MD, MPH:

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

