

Management of Mild to Moderate COVID-19 in People Who Are Immunocompromised

Introduction

Dr. Martin Witzernath (Charité – University of Berlin):

So welcome to this educational program titled COVID Rounds: Management of Mild to Moderate COVID-19 in People Who Are Immunocompromised.

My name is Martin Witzernath, and I'm the Head of the Department of Pulmonary and Critical Care Medicine at the Charité University Medicine in Berlin. And here with me, Cristina Mussini.

Dr. Cristina Mussini (University of Modena and Reggio Emilia):

Yeah, I'm Full Professor of Infectious Diseases, Chief of the Department of Infectious Diseases at the University of Modena and Reggio Emilia in Modena, Italy.

Dr. Witzernath:

And Michele Bartoletti.

Dr. Michele Bartoletti (IRCCS Humanitas Research Hospital):

Hi, everyone. I'm Michele. I'm Professor of Infectious Disease at the Department of Biomedical Science of Humanitas University and the – of Infectious Disease Unit at the Humanitas Research Hospital.

Patient Case

Dr. Witzernath:

So let's start with a patient case. We have a 45-year-old woman with recent diagnosis of mediastinal lymphoma, and she's admitted for febrile neutropenia and mucositis. She reports mild URI symptoms like cough and a sore throat that began two days ago.

Her vital signs are stable. She's stable on room air. Her medications have been EPOCH-rituximab. The last cycle was two weeks ago, acyclovir, fluconazole, levofloxacin and trimethoprim sulfamethoxazole.

Her vaccination status was that she was completed an initial mRNA series. She was boosted in 2021, and she had COVID-19 in 2022. So two years ago. And now she presents with a positive COVID-19 antigen test.

Current SARS-CoV-2 Trends

Dr. Mussini:

So let's talk now about the current SARS-CoV-2 trends.

CDC: Circulating COVID-19 Variants

First of all, it's important to look at the variants of concerns. So what are those that are circulating now?

As you can see from the most recent graph that in this picture, you can see that from a situation where there was, in a way, the – the domination of one of the VOC[?]. Now, in the most recent month, we have seen that the situation is more mixed up.

What is more important to understand is that all these variants, they belong to the same Omicron lineage. And this is very important because we know that Omicron really change the pattern of the disease because Omicron is very effective, so easily transmittable, but mostly it – it's - you know, it has – it's localized at the upper respiratory tract, so it can determine lower respiratory tract localization, especially pneumonia only in people who are really immunocompromised.

WHO: Variants of Interest and Under Monitoring in EU/EEA

Among the variants, there are a couple of variants that are for now under monitoring by EU and they – as you can see, they all are Omicron and the lineage are BA.2.86, KP.3 and XEC.

If you can see, we don't have a lot of evidence about these variants. And especially we don't have important information about the impact on severity because it seems that there is no impact on severity. So we continue to monitor. EU is continuing to monitor. But for now we don't have a specific alarm that has been raised.

COVID-19: Impacts on Vulnerable Patient Groups

As I said, in most of the people who are not immune-compromised, these variants determine a sort of influenza like syndrome, flu like syndrome with cough, with – you know, with cold, runny nose. But not what we have seen at the beginning with, for example, with Delta.

What we can see is that in vulnerable patients, the situation could be different because not only we have the acute infection that could also exacerbate chronic illness. Let's think, for example those with – who have a chronic broncho hepatic disease, for example. But also we know for now that after the acute phase is resolved, we can have a post-acute sequelae.

COVID-NET: Cumulative COVID-19 Associated Hospitalizations By Age Group and Season

The association of hospitalization with COVID. You can see since the beginning, we have seen that age was a major factor or severity in – in COVID – in COVID-19. But still today, we see – we are talking about from March 2020 to April 2024. Still today, we see that the older age is probably the most relevant factor that influence hospital admit – admittance. It will be important to discuss about it because many times COVID in these patients just represent the cherry on the top of other disease – diseases, other comorbidities, and not really a lung involvement.

INFORM: COVID-19 Outcomes in Immunocompromised and other High-Risk Populations in UK

Very important data arrived to us from the INFORM study, that is a cohort of immunocompromised patients follow in the UK. It's obviously a retrospective, but the numbers are very relevant. As you can see, we are talking about almost 500,000 immunocompromised.

And the immunocompromised that represented 3.9% of the study population, they accounted – despite the low number, I mean, of them among the general population that was affected by COVID-19. But they – they quoted for 21 – almost 22% of hospitalization for 25% of those who had more than three vaccinations. So it's not that they do not try to protect themselves, but unfortunately, they account for almost 24% of deaths and among also those who had more than three vaccination. So we are talking really about fragile – fragile population.

INFORM: COVID-19 Outcomes by Population

Many of them when we look at the outcome, the – the risk was very relevant for all of them. But we could think about, for example, the risk is extremely high in those who had a transplant – a bone marrow transplant. And – and also in those who have a solid organ transplant.

So we have to consider, even when we talk about the risk in immunocompromised, that their – that immune compromise could differ. And the one with the highest risk are those who are taking anti-rejection drugs, those who had a bone marrow transplant or hematopoietic stem cell transplant, and those who had a solid organ transplant.

Patient Case

Dr. Witzenrath:

45-year-old woman with the recent diagnosis of mediastinal lymphoma with mild URI symptoms that began two days ago, who is stable on room air, has stable vital signs, had immunosuppressive therapies and has now a positive COVID-19 antigen test, despite a proper vaccination status and a prior COVID-19 infection.

She's admitted to the ward and initiated on IV vancomycin, on cefepime and micafungin for febrile neutropenia and continued on acyclovir. And obviously now the question is should any COVID-19 therapies be initiated in this specific patient?

COVID-19 Diagnostic Workup

But before we consider the therapy, we might want to do our COVID-19 diagnostic workup. And of course, it's of utmost importance to assess the severity of the disease and to reflect on risk factors for progression to severe COVID-19 in such a patient.

We need lab testing. We already have a positive antigen test. We might consider PCR. We obviously need a CBC with a differential. We need a CMP and maybe other labs depending on the specific patient.

We might want to have a chest CT to get an idea of the lung infiltration and an EKG, maybe other studies, depending on the specific patient.

Assessing for Clinical Severity and Worsening

Now how are we going to assess for clinical severity? Most patients who enter the ER get a qSOFA done that includes a new onset of a confusion or GCS, Glasgow Coma Scale below 15 and a respiratory rate of more than 20 breaths per minute, and a systolic blood pressure below 100 millimeter mercury.

For each of these criteria, you might give this patient one point in the queue. So far, however, this falls too short because in a typical patient with COVID-19, we frequently observe this sort of happy hypoxia. So patients do not realize that they have a low oxygen saturation. And they might have an oxygen saturation below 92% at room air, which would reflect a rather severe course of the disease already at that time.

Moreover, particularly older patients or weak patients may not be able to produce higher respiratory rates, although they might need these higher respiratory rates to oxygenize their blood. So oxygen saturation again might be reduced in these patients.

And then it's important to look for $p\text{CO}_2$ because lower $p\text{CO}_2$ levels might reflect hyperventilation. And serum lactate levels that are increased might reflect beginning of sepsis. These are unfavorable – unfavorable symptoms or changes that you need to consider.

And then it's important to not only have a one-time measurement, but to consider unfavorable trajectories and do these assessments again and again over the next hours and days.

Of course, also acute renal failure may reflect clinical severity, and it's important to reflect on comorbidities of these patients as patients with pulmonary comorbidity or cardiovascular comorbidity or other comorbidities might experience more severe cases of COVID-19. And then, most importantly, severe immune suppression may increase the risk for a unfavorable trajectory.

COVID-19 Treatment Recommendations

So let's go to the COVID-19 treatment recommendations. And here we have to consider the course of the normal COVID-19 infection.

Management Strategies for COVID-19 Infection

And this is that the patient comes in mostly with mild symptoms or maybe moderate symptoms. And at that time he has already been infectious. And then the disease may progress to severe case. And we do have a lot of possible medications for these patients. We might consider antiviral drugs like nirmatrelvir, ritonavir or remdesivir in inpatients. We have to consider inpatients with hyperinflammatory situations that immunomodulators might be beneficial like dexamethasone, cytokine inhibitors or junk inhibitors. And we have to talk about anticoagulants. And we will consider all these medications in a minute – in a minute.

And then if the patient gets more severely ill oxygenation might be important or even mechanical ventilation like – and also hemodynamic support or other adjunctive therapies.

Evolution of COVID-19 Guidelines

Dr. Bartoletti:

So talking about treatment, we probably should focus on current COVID-19 guidelines. And you probably know that there's a lot of scientific committee and society that develop their own guidelines as may develop guidelines into 2021 and 2022. But unfortunately, they are not updated now.

WHO guidelines updated the last version of guidelines in November 2023. And the NIH and IDSA guidelines are the one that are most updated that were recently updated in the last time in August 2024.

We are expecting new documents of ESCMID talking about management of COVID-19 in immunocompromised patients.

We – when we talk about guidelines, we probably should focus on typical patients that were included in randomized controlled trials that were – were used to build the guidelines. I think that the most evidence came from the very early phase of the pandemic when the most common patients that were enrolled in a randomized controlled trial were 60 or 70-year-old, obese with hypertension, diabetes.

I think that, as Cristina said before, these are not more patients that we see in the current clinical practice, and we are now focusing more on elderly patients or immunocompromised patients.

So when we talk about guidelines and the recommendation on guidelines, I think we should probably know that the population used in the randomized control trial that were used for guidelines are not the population that we see now.

So I think we should briefly discuss altogether which COVID guidelines we use in clinical practice. And probably if we still use some guidelines, we prefer to adapt our own protocol in our institutes.

I think that in – I, generally speaking, follow IDSA guidelines which are the most updated, even though in the current guidelines I said before, the guidelines do not focus on immunocompromised patients. We know that immunocompromised patients were not included in the – in the – in the most common trials, so we are not available to say something about randomized control trial in this setting.

Beyond the randomized control trial, there's a lot of real world evidence showing that there's some beneficial of some treatment, additional treatment for immunocompromised patients, especially for example, combination treatment of one or more antiviral.

So I think that we – generally, in my institution, we follow guidelines, IDSA guidelines, but in very specific situation we go beyond guidelines and adapt with the more recent literature. I don't know what about Cristina?

Dr. Mussini:

Yeah. No, I perfectly agree with you. I think that it depends on the reason why we should treat someone with COVID-19. I mean, I think that if the clinical picture is rapidly progressing and it seems like the patient is not controlling the infection, and we see that the symptoms are becoming more and more severe. So that's why – that's when we really treat COVID-19. But in most of the cases what we do, we treat it for practical reasons.

Let's say that the patient has to undergo a cycle of chemotherapy, for example, and that the hematology don't want to treat someone who has a positive swab. We treat with everything because actually it's like saying abracadabra, because there is not one of the drug that has shown to reduce the time of the positivity of the swab in a very significant way.

So usually we start with one. If it doesn't work, we start with the one with less drug-drug interaction. And then maybe we add another one. And so it's – it's not something that we really treat fortunately now COVID-19. We treat the positivity we could – because it could have an impact in the management of the underlying disease or the patient more than of COVID-19.

I don't know your experience, Martin.

Dr. Witzzenrath:

Yeah. Well, I mean, in general, we do, as Michele said, follow the IDSA guidelines. We also have specific German guidelines on the treatment of COVID-19. And we do have a recommendation of the German Robert Koch Institute. That's called COVRENE[?], very helpful web page where you get advice.

But of course, in – in these specific, very immunocompromised patients that need treatment, I mean, you would want to have the patient on the treatment for the underlying disease as soon as possible again. And as you said, Cristina, I fully agree. You would like to use all possibilities that you can use to – to get rid of the virus and to get the patient back on track.

NIH COVID-19 Guideline Recommendation

Dr. Bartoletti:

We talk about several guidelines, and – but we will do just a rapid overview about them. So in the NIH COVID-19 guidelines recommendation, for ambulatory settings, we generally – steroids are not recommended, but antivirals are highly recommended because they've shown that can reduce hospitalization and death for – for COVID-19.

And generally the most common antivirals are recommended are nirmatrelvir, ritonavir or remdesivir.

Molnupiravir could be considered as an alternative, but in most countries, not available anymore. For example, in Italy we cannot use molnupiravir right now because it's – it's out of – of – of availability of – of drugs.

In hospitalized patients, generally we stratify the treatment according to the needs for - or oxygen therapy and the patients who do not need oxygen or supplemental oxygen therapy, steroids are not recommended because they can also in paradoxically get – worsen the course of – of COVID-19.

Only in patients at a risk of progression, guidelines suggest remdesivir. Remdesivir is also suggested in more severe cases when patients especially needs oxygen therapy or non-invasive treatment. But generally they're not highly recommended in patients receiving mechanical ventilation or ECMO. But guidelines suggest to consider remdesivir as a special situation.

Obviously, in this phase, as Martin already said, we need also anti-inflammatory drugs. So dexamethasone is the most recommended as the initial treatment for all patients and needs supplemental oxygen, but especially in patients with rapid progress to more severe cases baricitinib or tocilizumab can be considered as additional treatment.

IDSA COVID-19 Guidelines Recommendations for Hospitalized Patients

I think that ID – IDSA guidelines are pretty similar to the previous. They consider to use all in severe cases, dexamethasone, remdesivir, and especially baricitinib or tocilizumab in rapidly progressing patients or the patients who are in the – in a critical situation.

Risk Factors for Progression

Dr. Mussini:

We have seen that remdesivir is indicated for those who are at risk for rapid progression, but who are these people who are at risk for rapid progression?

Risk Factors for Progression to Severe COVID-19

So if we look at the risk factor, some of them, that really dates back at the beginning of the epidemic. So because the age, as I said before, has always been associated with a worse prognosis, but also medical condition. If you remember all the cases with diabetes, with hypertension that here is not listed. But I remember in the first paper by the Chinese authors, hypertension, it is so common, was one of the worst risk factors, but also kidney disease, obesity. Unfortunately, how many people, also very young but who were obese, died of COVID-19 during the first phase of the pandemic. And then also pregnancy.

Obviously, we are talking about a virus that has been defeated by its mutation, I would say, because it has become less, you know, prone to go to the lung, but also especially by the vaccination. So this vaccine or state – the – the status of the vaccine of the patient is very, very important.

And it's important to understand how many – how many doses the patient had. And then this – the status of the immune system, because as we have said, higher risk in people that are immunocompromised or receiving immunosuppressive medication, for example, those with anti-rejection drugs.

Immunocompromised Individuals Are at Elevated Risk for COVID-19 Infection and Complications

So which are the immune-compromised who are at elevated risk for COVID-19 infection and complication?

Those who are at high risk, obviously, are those with a lung functionality that is in a way compromised. So severe respiratory disorders, some rare blood disorder, rare metabolic disorders, diabetes treated with insulin, significant developmental disabilities, pregnancy with serious heart condition, neurological impairment. All these situations could be listed. For example, for flu could be listed for severe bacterial pneumonia.

I mean, there are – these people have such a, you know, a situ - a clinical situation that is so compromised that an acute illness could determine really a severe disease, even if in immunocompetent people it doesn't end up like this.

Then we have moderately immune compromised. So cancer. We have seen in the previous slide that I showed you that cancer had a higher – cancer patient had a higher risk of severe disease, but not comparable with other situations like bone marrow or stem cell transplant or solid organ transplant. So we are talking about a moderate risk.

Immunosuppressive therapies. HIV, there has been a huge discussion about HIV less than 200, but especially those who are like late presenters. So not with an undetectable viral load because we really have seen even during the pandemic very rarely, patients with this situation. And moderate primary immune deficiency and dialysis or severe renal disease that we have seen so many patients in dialysis or severe renal disease.

But who are the ones that are really at higher risk of a bad prognosis, are the ones with hematologic malignancies with the active treatment, stem cell transplant, anti-CD20 agents and B-cell depleting therapies, solid organ transplant, severe primary immune deficiency.

Adults With Malignancies Have Elevated Risk of Hospitalization and Death From COVID-19

Those who are severely immune-compromised are really those that – where we should not lose any time, I think, in prescribing antivirals. But we have to think also about antiviral treatment in the other two previous conditions. So, you know, moderate and medium risk because we know that, for example, we talk about cancer and we have seen that, for example, as you can see, if someone has no cancer, the risk of hospitalization or mortality is almost non-existent.

When we go to solid organ, there is a, you know, a higher rate of hospitalization and a very little higher risk of death compared to the general population with no cancer. But it's when we go to hematologic malignant neoplasm that we see the difference in a statistical difference.

Multiple Factors May Affect Vaccine Efficacy in CLL and Other Lymphoid Malignancies

So there are multiple factors that may affect why they are at risk. If we are talking about these patients who are severely immune-compromised, we know that they vaccinate. They do a lot of doses. They do all the – you know, all the possible doses that they can. But unfortunately, when you are immune-compromised, your response to vaccine is impaired.

And there are multiple fact – factor that may affect vaccine efficacy in chronic lymphocytic leukemia and in other lymphoid malignancies. There could be vaccine factors. So those intensity and frequency if they don't vaccinate – vaccinate. The patient factor, age, comorbidities, hypogammaglobulinemia – hypergammaglobulinemia.

Treatment factor, like you know also doctors they say watch and wait. Or maybe they have been previously treated and all these factors that is a reduced number of people that mount an immune response there is still a need there. We have to understand if the antibody titers are protective or not, how much do they last? So if there is a persistence of these antibodies. And the result is that there is a reduction in the clinical incidence of infection in a way.

I mean, if we can provide this patient with some other, for example, protection, as we did with the antibodies that now are not used anymore, but we did the monoclonal antibodies in many of these people, in many of these populations. But now we don't have very effective ones, so we don't use them anymore. But the only way to reduce the clinical incidence of infection in those who could not respond to vaccine is to have alternative strategies.

I have talked about how to determine patient at high-risk for COVID-19 progression. So what do you do? Does it matter how immunocompromised they are? What are other criteria aside from immune-compromised that you consider for example being old or other risk factors? What do you do?

Dr. Witzzenrath:

I think – I think here we can rub up a little bit what we just said and heard. And I mean, obviously age is an extremely important risk factor and the comorbidities are. And of course the question how immunocompromised is the patient?

And if there is no B-cell and T-cell response, then this patient might be in a very high risk situation. That's the general perspective. And then of course, we have to look at the patient in a personalized way. And as I said, look for the Quicksilver criteria, the oxygen saturation, the pCO2 serum lactate question, whether the patient has renal failure or other comorbidities.

And then, of course, the question how immunocompromised is the patient? But maybe Michele wants to add here.

Dr. Bartoletti:

Yeah, I totally agree with you and with Cristina. I think that as previously said, when we talk about immunocompromised patients, we have to consider which is the underlying disease, but also which is the – the program of treatment, because I think that, as said Cristina, we have also to consider that the patient needs continuous treatment.

So besides underlying disease, also we have to consider the program of the patient. And additionally, all treatment should be considered. And probably now what we're seeing, especially in hematological patients is that a lot of different treatment the day they go. For example, lymphoma patients, they can receive standard chemotherapy. Then they go autologous transplant. And then the – the – they go to CAR T treatment.

And then they can fail a CAR T. And they have – still have bispecific antibodies. And then again allogeneic transplantation. So I think all these can have a – really all together can higher really the risk factor for – for COVID progression.

So again personalized treatment according to patient history and – and clinical features are very important – is very important in my opinion.

Dr. Mussini:

Yeah.

Dr. Witzzenrath:

I think that – that point, if I may add, that we have to consider to – to – to talk to the people who are – to the colleagues who are dealing with the patient and their general underlying disease. So in our specific patient, we obviously would like to speak to the hematologist and ask how important is it now to continue the therapy? How quickly do we have to get back on track? Do we have some – some time to react here? And what's the perspective of this patient? So the – the multidisciplinary approach here is particularly important I guess.

Dr. Mussini:

Yeah, I was thinking also in the compensated diabetes, for example. So it's important not only to think about, you know the intensivist, I mean, or the neurologist, but also to think, you know, at all the other comorbidities that could have led to a severe picture. So I think that this is very important, as you said, the multidisciplinary approach. Michele.

Remdesivir

Dr. Bartoletti: Yeah. We talk about guidelines, our approaches, what we follow. But let's talk about drugs, because we treat patients with drugs, obviously. And I think we should focus a little bit on antivirals because nowadays, probably according to what Martin said, that what we see, especially in immunocompromised patients, a patient that we see with a large – high viral load and a very initial phase of the – the – the disease, less patient with severe disease that probably needs anti-inflammatory drugs. So we should probably focus more on antivirals right now.

Remdesivir Landmark Trials in Hospitalized People With COVID-19: Baseline Ventilatory Support

So the first drug I'm going to talk is – is remdesivir. Remdesivir probably you know because it's one of the first drug we use for treat COVID-19. And as you probably know, there's – this drug was – was uncensored after conducting several randomized controlled trials with conflicting results, I would say, and especially from SOLIDARITY, which initially said that probably remdesivir has no efficacy on the patient, whereas some other ACTT, DISCOVERY show the benefit on the treatment with this drug.

I think, again, we have to consider which patient were enrolled in the trial, especially in the initial phase of the pandemic, which are – where patients that were, I think, advanced patients with a long story of symptoms with no treatment. And probably this also have the condition in the results of the trials.

However, beyond the clinical trials that with meta-analysis showed that this drug is very effective and treatment – in treatment of COVID-19. Probably we have to consider now the population how is different from those hospitalized – from those hospitalized today.

So briefly can we discuss a little bit of how the COVID treatment evolved from – from the early phase of the pandemic to today? I think that as said before several times, probably the population is different, the COVID is different, the variants are different, and the population and the risk is different.

So Martin, do you see a lot of patients that are nowadays admitted in the ICU that needs tocilizumab or baricitinib, high dose dexamethasone or whatever?

Dr. Witzelrath:

I mean, most of the patients we do see now are not the patients that we saw in the early phase, obviously. So we very rarely see patients that had – have not have had another COVID-19 episode before and that are naive to COVID-19 vaccinations. So most of the patients we see with a severe course are either immunocompromised or have an additional bacterial infection or any other circumstances, like severe comorbidities that are deteriorating under a rather normal viral infection by SARS-CoV-2 in this case, then.

So there's – there are not many patients that receive like tocilizumab or baricitinib anymore in our words. Dexamethasone from time to time, depending on the specific case. And particularly because we also know from the Severe CAP trial that has been published last year that dexamethasone may be beneficial or hydrocortisone in this case may be beneficial in Severe Community-Acquired Pneumonia anyway.

What about the situation in Italy?

Dr. Mussini:

Yeah. No, it's the same, you know. Usually people – most of the cases, people arrive in at the emergency room for other causes. It could be cardiac decompensation. It could be pneumonia, bacterial pneumonia. And then they do the swab. Because every time you have a respiratory symptom, they do the – the swab and it's positive and they arrive to us. So it's very, very – I mean, apart from some steroids, as you said. But for the rest, I think that we did during this year, 2024 once tocilizumab in a non-vaccinated person. But, you know, it's in a way we think that Omicron is less pathogenic.

But the problem is that we – we don't know because everybody has already had or several shots of vaccine or several infection by SARS-CoV-2. So we really don't know. But if someone didn't acquire the infection and was before – and was not vaccinated, we – we saw that you could end up in with a severe interstitial pneumonia.

So I think that – but in the vast majority of cases, we just wait until the swab is negative and then we transfer them to – to other wards, like internal medicine or whatever.

Remdesivir for Immunocompromised Patients Hospitalized With COVID-19 Across Variant Waves in US

Dr. Bartoletti:

As said before, most randomized control trial did not include immunocompromised patients. And I think it's very important to see what the real evidence study shown about this topic, especially what the efficacy of remdesivir in this group of patients hospitalized with COVID-19.

So this is an interesting study that was published in Clinical Infectious Disease in 2023, showing that when patients are immunocompromised and are treated with remdesivir, there is a reduction on overall mortality in all – across all variants wave in the US. And this was confirmed for 14 days mortality and 28 day mortality.

So again, we can say that this drug in the real world evidence seems to show a very high benefit to these patients.

Remdesivir for Patients Hospitalized With COVID-19 Not Requiring Oxygen in US

And also, what about patients that are hospitalized with COVID-19 not requiring oxygen because guidelines – this is something a sort of a gray zone in which guidelines not necessarily suggest to use antivirals, but just to wait to patient that became more severe and – and needs oxygen to start antivirals.

But it's very strange because if we – the patient will benefit from the early stage when they are outpatient of remdesivir, why not they should not receive remdesivir also when they are hospitalized but not require oxygen.

So this study that is more recent to the – and was published in 2024. And these are retrospective multicenter study of adult hospitalized with COVID-19 or requiring supplemental oxygen that receive remdesivir within two days from admission. And overall, this is a very large database that the authors demonstrated that the patient receiving remdesivir have an estimated reduced relative mortality risk reduction of overall 17 that was confirmed in the pre-Delta, in Delta and Omicron periods.

So – and this was also confirmed in just analysis with Cox regression. And so adjusting for all possible confounders.

Dr. Mussini:

Before talking about nirmatrelvir, ritonavir, I just want to make a comment with the two of you, because, you know, COVID-19 has been described as a two phases disease – two phase disease that is, you know, first is the viral phase and then the inflammatory phase, and then one in between.

But you know, so it's not surprising for me that remdesivir, as all the other antiviral – antivirus could work in the first phase, is less explicable in the second one. But I think that in immune-compromised, there is – the viral phase never ends because the immune system could not control it. So you continue to have an activity of antiviral even during the inflammatory phase, because the virus is still there. I don't know, what do you think?

Dr. Bartoletti:

Yeah, totally agree with you. I think that the viral phase in immunocompromised patients is never ending. So what we're seeing, especially in the severe immunocompromised patients or patients receiving anti-CD20 treatment, that the – the viral phase is something that that persists for months and months. And sometimes they progress to also to have severe pneumonia after – after several weeks from the initial infection.

Dr. Witzenrath:

Yeah. Totally agree. Sure. Particularly in those that are severely immunocompromised. I mean, it obviously makes sense to test for the viral load from time to time also to monitor your therapeutic efficacy, but therapy success. But yeah, I absolutely agree.

Nirmatrelvir + Ritonavir

Dr. Bartoletti:

So beyond remdesivir, we also have some other drugs, especially other antivirals.

EPIC-HR: Nirmatrelvir + Ritonavir for High-Risk, Unvaccinated, Nonhospitalized Patients With COVID-19

Nirmatrelvir-ritonavir is another important drug that was – was licensed just a few months after remdesivir. And thanks to the EPIC study that demonstrated that nirmatrelvir-ritonavir for patients that are not hospitalized with COVID-19 did show a really good effect on – on preventing hospitalization and death.

However, when the second study was done recently and this was published in – in 2024, a new study that was focusing on fully vaccinated patients and patients with standard risk, the early treatment was not more associated with any effect in terms of hospitalization and mortality.

And as you can see, the – this is because the rate of hospitalization in patient – patients receiving placebo was so low that they could not demonstrate a difference in terms of treatment effect.

So probably, as said before several times, nowadays the landscape of treatment has changed a lot with vaccination with previous infection, and probably now patients with standard risk has not more need for such antiviral treatment compared before.

So probably we should focus more on very severe immunocompromised patients, fragile patients, early patients and patients with multiple comorbidities rather than standard risk patients.

Nirmatrelvir + Ritonavir: CYP3A Metabolism

When we use nirmatrelvir-ritonavir, which is still very useful for – for the patient with high risk, I think we should comment on possible drug-drug interaction, thanks to the metabolism to – to the cytochrome CYP3A. And then I suggest everyone that want to start to use this drug to check for drug interaction. These are multiple websites you can check all the drugs that can be prescribed together. And sometimes contraindicated, sometimes you can use with caution when these two drugs are used together.

I think in the majority of cases, all the drug interactions are manageable. For example, if you use statins, you can just discontinue statins for a few days while the patient receiving the drugs. But in other cases, especially when we use anti-cancer drugs or anticoagulants or immuno or immunosuppressive treatment. So I suggest to check in any patient all possible interactions.

So let's discuss a little bit. I think we should go back to the patient that was presented initially during this webinar. And what would be your approach for this patient? Cristina, you want to start?

Dr. Mussini:

No, I mean, I think that the problem is that I think that this person has a high risk because she's very immunocompromised. She is – you know, she is the part of the severe immune compromise. And you know despite the fact that she had multiple shots whatever, but her clinical situation was worsening, so I would – I would go for the antiviral and I would go for remdesivir. And you, Martin?

Dr. Witzernath:

Yes. Well, as she has been admitted to the hospital as she is on IV drugs anyway, I would agree. I mean, if she stabilizes, if she can be discharged then and still has viral load you would maybe want to then change to nirmatrelvir-ritonavir. But as you said before that I would personally check. And I very much like this Liverpool drug-drug interaction checker on the web page.

IDSA and NIH Recommendation

Okay. So either remdesivir or nirmatrelvir-ritonavir. Based on IDSA, NIH guidance or both drugs can be used. In this case, probably we will go to remdesivir because the patient was admitted and has an IV. But we have to consider that both drugs are very effective in controlling SARS-CoV-2, especially to preventing progression to severe disease.

Key Take-home points

Dr. Bartoletti:

So we have some take-home points. So treatment of COVID-19 hospitalized patients depends on the severity of disease and the risk for progression. And I think that some important factors should be considered in selecting those patients who may need early treatment, especially immunocompromised patients or patients with other risk factors for developing severe COVID-19.

We know that patients included in the earlier randomized controlled trial are now are much different from those that are hospitalized – hospitalized today. So we – it's very difficult to – to transfer all the data to the current situation. So we need to consider real world evidence studies, especially emerging data in people who are immunocompromised patients.

And also we have to consider that especially in patients with mild to moderate COVID-19 who have risk factors for progression to severe disease, remdesivir or nirmatrelvir-ritonavir or both, in some situations can be considered. Remember to assess for drug-drug interaction when used nirmatrelvir-ritonavir in your patient.