

COVID Rounds: Inpatient Management of Patients With Severe and Critical COVID-19

Introduction

Dr Stephen Cantrill (University of Colorado):

Welcome to this educational program titled Covid Rounds: Inpatient Management of Patients with Severe or Critical COVID-19.

Faculty

Dr. Stephen Cantrill (University of Colorado):

My name is Dr Steve Cantrill. I practiced emergency medicine for 42 years at Denver Health Medical Center. I'm joined by 2 of my colleagues. Dr Gandhi, would you like to introduce yourself, please?

Dr Rajesh Gandhi (Harvard Medical School):

Sure. My name is Raj Gandhi. I'm at Massachusetts General Hospital and Harvard Medical School in Boston. It's a pleasure to be here.

Dr Cantrill:

And Dr Patel?

Dr Payal Patel (Intermountain Health):

Hi. My name is Payal Patel. I'm an Infectious Disease Physician, and I work at Intermountain Health.

Dr Cantrill:

Thank you.

Initial Framework: COVID-19 Workup in the ED

So let's start. Most patients, especially those that are severely or critically ill, will come through the emergency department in your hospital. So I'm going to review what we do in the ED to evaluate and care for those patients. So first we would talk with the patient and get their story.

Patient Case

Now, this is a 45-year-old woman who has a remote diagnosis of mediastinal lymphoma who received rituximab containing chemotherapy in the past, presents to your ED with fever, myalgias, cough, and other URI symptoms with a 2-day duration. Her vitals as shown: blood pressure 90/56, heart rate 120, respiratory rate 22. Her temp is 39.2 orally, and her O2 saturation is 90% on 6 liters via nasal cannula.

Her physical exam is remarkable for bilateral crackles on the lung exam. Her medications include EPOCH-rituximab. Her last cycle was 1 year ago.

Her vaccination status. She did receive 2 doses of the mRNA COVID-19 vaccine 3 years ago. No booster doses. She reportedly had COVID-19 approximately 2 years ago. She did do a home COVID-19 antigen test, which was positive.

COVID-19 Workup in the ED

Now the workup in the ED. First, our goal is to stabilize the patient and then assess the severity of the disease and also the likelihood of this process worsening. We will complete the workup, begin treatment if indicated, and then determine the proper disposition, either home with follow up, a ward admission, or intensive care unit admission.

This lady has a relative hypoxia, and you may want to consider high-flow nasal cannula in this patient or some noninvasive ventilation, either BiPAP or CPAP, or in the most dire circumstance, endotracheal intubation, if necessary.

She also has probable hypotension. We don't have old records yet, so we can't tell. And she has a tachycardia and a fever.

COVID-19 Diagnostic Workup

So our workup is standard history and physical assessment of the severity of the disease. Look at risk factors for progression to severe COVID-19. Although this lady, as we will find out, is probably already there. In terms of lab testing, we would want to repeat the antigen test or the nucleic acid amplification test, a complete blood count, a complete metabolic panel, a liver panel, a lactate, a C-reactive protein, a pro time, a D-dimer, and any of the labs as indicated.

In terms of chest imaging, this lady would certainly require chest imaging. And given how sick she is, I would probably, if possible, opt for a chest CT. Although some places where they have the technology are using point of care chest ultrasound to ascertain the severity of the disease, looking for B-lines or pleural changes. An EKG and any others that might be indicated would be performed as well.

Considerations for Pulse Oximetry

Just a side note about pulse oximetry. There are considerations about that. We rely on it a lot, especially in the emergency department, but it can be altered by skin pigmentation, skin thickness, skin temperature, and many of the pulse oximeters that the lay public use at home, in fact, are not FDA approved. So you do have to question their accuracy.

Patient Case

So for this patient, we do have some results back. Her CBC and CMP are unremarkable. Her CRP is elevated at 8.5 mg/dL. The chest CT shows bilateral ground glass opacities with some consolidation in multiple pulmonary segments. So this lady obviously is quite ill.

In terms of risk stratification, the NIH does have a severity classification. And you can see here that this lady is not—she's in severe. And in fact, I would argue that she's critical. She has impending respiratory failure and managing that is going to be a challenge.

PRIEST COVID-19 Clinical Severity Score

There was a tool developed early on in the pandemic. It's called the PRIEST score. And what it is, it's a COVID-19 clinical severity score that gives you a look ahead in terms of the likelihood of the patient becoming more severely ill. And you can see, the nice thing about this score is it doesn't require any imaging or any lab data. So you can do it early on in the patient encounter to determine especially helpful with mild and moderate cases.

So this lady, you can see her total score is 17, which means that she has a 66% chance of deterioration. Although, she's obviously quite sick already.

COVID Patient Disposition

So this would put her in a critical category. So she is going to be admitted to the intensive care unit.

Now things to think about. One of the things in the ED that I am always concerned about is a patient that's this sick getting the treatment started early on, not waiting till they get upstairs. But if I can get things going quickly, working with my consultants. So we're all on the same page in terms of what drug regimen we're going to start? I think that's very important.

Dr. Gandhi:

I would agree. You know, we'll review some data shortly. But I think the earlier you start treatment after symptom onset, the more likely it's going to be effective. That's certainly true for antivirals and not just in COVID, but in many conditions. Let's use influenza as an example. The sooner you start treatment, the better.

So I know in my emergency departments, sadly, some patients sometimes wait for more than 24 hours before they get upstairs. Not this kind of patient because she is very, very –

Dr Cantrill:

Sick. Yeah.

Dr Patel:

Yeah. I think it maybe highlights having easily accessible whether you're using internal stewardship guidelines or whatever document the hospital is using. There have been so many reiterations of, you know, what is the treatment for COVID-19. And we're in a new era now where the last document may have been updated months ago, maybe even a year ago, and it may be a new provider may not know where that is. So I think this is, you know, really highlights how important it is both for the ED, potentially for urgent care and for the stewardship team to have that readily available.

Dr. Gandhi:

Couldn't agree more. You know, there was a time when we were doing this every single day now. It's perhaps not every single day. And so making sure that we're not using an out-of-date guidance that that might be from 2022 or 2021. This was a case where things were really changing at some point, really by the - by the week. And so having those up to date guide - guidelines is really critical.

The NIH of course had guidelines for several years those have been sunsetted. So where I think I go right now is either my institutional guidelines or the IDSA guidelines. Those are kept up to date.

You know, Steve, you mentioned one thing about your consultants. I think maybe I can just put in a plug for a multidisciplinary approach here. This is where essentially you're going to have pulmonologists working hand in hand with the ED and working hand in hand with infectious diseases. And so it really is not just one. The nature of COVID, especially severe COVID, is a multidisciplinary consideration because in terms of how to support the person with oxygen when they need noninvasive ventilation, so pulmonologists are the right people to work with the ED on that. And then infectious disease really has its role around antivirals. And really it's comments about immunomodulatory therapy.

This patient may even have a role for her oncologist and others who will know about the nature of her her immune compromise.

Dr Cantrill:

Right. And I think it's good care to try to get everybody on board as quickly as possible.

Dr. Gandhi:

Not this early on. But this patient did get immunized perhaps in 2021, 3 years ago or so, didn't get boosters after that and then had COVID 2 years prior. She will have some amount of hybrid immunity. But we've also learned that some of that will wane and may wane more rapidly than someone who's gotten a drug like rituximab, which will affect the ability of the B-cells to make antibodies.

So I think, I would say pretty much everyone at this point is either have been vaccinated, had COVID, or most likely had both. But there is some importance to the timing of those because at least with vaccines, the biggest boost you get in antibodies is in that first few months. T-cells probably do stay around, but that's where her chemotherapy, perhaps she had steroids as part of EPOCH.

In fact, I think that the EPOCH is prednisone. And so she probably has had a hit to her T-cells as well.

COVID-19 Treatment Recommendations

Let's move on now to COVID-19 treatment recommendations. Dr Patel?

Dr. Patel:

Yeah, thank you so much. So we'll start with thinking about really the continuum that patients can present and really continue on as they have COVID infection.

Treatment Across the COVID Spectrum

And I think that's really important in thinking about how the different treatments that we have available work. Thinking about early on in illness, when you're potentially having asymptomatic infection or mild illness, that's when viral replication is often at its highest, and where a drug like remdesivir would potentially be most effective.

As a patient continues to potentially get sicker and become moderately ill, or severely ill or critically ill in the ICU, needing potentially mechanical ventilation or ECMO, at that point, the way that COVID works is it really hits off this inflammatory cascade and hypercoagulability. And at that point, the evidence or the need for treatment is really to focus on that inflammation cascade and try to prevent thrombotic events as well. So that's, I think, a really good way to start thinking about the current treatment recommendations.

IDSA COVID-19 Guidelines Recommendations for Hospitalized Patients

So here's a nice graphic of the IDSA COVID-19 guidelines. They have bucketed patients into mild to moderate for severity of illness, severe and critical. And going on into severe and critically ill. So once the patient is requiring supplemental O₂ or they're sitting below 94%, that's when steroids dexamethasone comes into play, remdesivir. And then depending on whether they're presenting with elevated markers of inflammation, thinking about baricitinib or tocilizumab. And then in the critically ill—these are patients who are going to be in the ICU. They're often mechanically ventilated or on ECMO and have evidence of end organ dysfunction.

In the IDSA guidelines, remdesivir is not present in this group. We're going to talk about some of the evidence about that. Steroids are still recommended. And again, if there's evidence of elevated markers of systemic inflammation, baricitinib or tocilizumab. Some things to think about with those, and we're going to talk about that in the next section is, you know, whether they can tolerate PO or IV, what is available in your hospital, and more recent evidence about which one may be preferred in these immunomodulators.

NIH COVID-19 Guideline Recommendations

These are the NIH guidelines, and they have a different—so again, thinking about the buckets that they have presented for severity of illness going from the top to the bottom. There's the ambulatory setting. So someone who's not hospitalized or someone who's hospitalized for something else. We talked about this in the very first presentation that we did. Maybe someone comes in potentially with an orthopedic injury and happens to have COVID. That person should probably be treated as if they are outpatient.

Once you're hospitalized and needing O₂, dexamethasone is recommended. Remdesivir is recommended, and if the patient is having rapidly increasing O₂ needs or evidence of systemic inflammation, that's when one can start thinking about immunomodulators such as baricitinib or tocilizumab.

And then as the patient gets sicker or is sicker on high-flow O₂. Again, similar recommendations. Once they're on mechanical ventilation or ECMO, in this group of recommendations it says to consider remdesivir. And then of course the anticoagulant recommendations which I'll go into in the next slide.

NIH COVID-19 Guideline Recommendations: Anticoagulation

So thinking about anticoagulation, there is a ton of work in this area by different international groups, primarily by pulmonologists in the ICU. Again, thinking about that hyperinflammatory cascade, there just is evidence that once that inflammatory cascade kicks off, there is more evidence of thrombosis.

Now, just taking a step back from this, I think it's really important to think about bleeding risk when you're thinking about these patients. And so that is—you know, you're sometimes you're between a rock and a hard place thinking about these again, starting from the beginning, thinking about someone who is in the outpatient setting or hospitalized for a non-COVID-19 reason. They would be coagulated just like anybody else on the med surg wards. And so that would just be potentially a prophylactic heparin dose unless contraindicated.

It gets more intense and really, you know, need to be thinking about what kind of anticoagulation you're using in that patient population. There's a separate group of guidelines for pregnant patients if you do have a pregnant patient. And so if the patient is hospitalized, needing O₂, hospitalized on high flow O₂, and then if hospitalized and in the ICU on mechanical ventilation or ECMO, these are really the recommendations from the NIH COVID guidelines. And you'd be thinking about a therapeutic dose of heparin in many of these patients, again, considering the bleeding risk on an individual case by case basis.

Remdesivir

Now, going into remdesivir and some of the evidence behind why the guidelines can be a little bit different, and you may have differing internal guidelines in your hospital as well. So to talk through why that may be.

NIAID ACTT-1: Study Design and Efficacy Outcomes

So going back to 2020. This was the big adaptive trial done by NIAID ACTT-1. This was a multicenter, placebo-controlled, adaptive, double-blind, randomized trial. They looked at adult patients and they did remdesivir vs placebo. And really the primary outcome was median recovery time, how quickly did someone get better when they had remdesivir vs placebo.

And there seemed to be a 5-day difference when patients had remdesivir. And so early on, you know, remdesivir was recommended really widely for these patients.

NIAID ACTT-1: Subgroup Analyses

And as you know, we continue to have more and more work, there have been more and more gray area and shadations to what we see. In this group, looking at the subgroup analysis, the benefit of remdesivir was clearest in those with symptom duration that was less than 10 days and on supplemental oxygen, but not intubated.

So again, thinking back to that first graphic that we looked at, thinking about how remdesivir works, the biological plausibility. You know, remdesivir is stopping the virus from replicating. And if we know that earlier on in disease, that's when viral replication is at its highest, that is probably when you're going to have the best chance of remdesivir being helpful to the patient.

So going back to the case earlier the better. If you know, if you have a patient who's rapidly getting worse, that may be someone to think about remdesivir early.

SOLIDARITY: Remdesivir for 10 Days vs Control for COVID-19 in Hospitalized Patients

This was a large WHO trial, again done very early on. I think it's really interesting to think about, you know, again, in March of 2020 or February of 2020 as this was being put together, we really didn't know what was going to work. And so when this study initially started, it was actually to evaluate remdesivir, hydroxychloroquine, lopinavir and interferon. And as you know, more evidence came in, really, remdesivir ended up being the main thing that this trial was looking at. So I think that's really important putting again, in context where this trial came from.

Initially, as the primary outcome that, you know, in SOLIDARITY showed that that there wasn't actually a difference in in-hospital mortality rates for remdesivir. But looking again into a subgroup analysis, it was found that the benefit for remdesivir is among patients who are not receiving mechanical ventilation at the time of enrollment, and that it showed a significant reduction in progression to ventilation in this group.

So there can really be some difficulty in understanding all of the literature that has come out and the way that we put it at our hospital—we have a fact sheet trying to describe what the evidence has been—is that there's often discordance between clinical trials and then real-world retrospective studies regarding the benefit of initiation of remdesivir and those already receiving mechanical ventilation or ECMO. And that leads to that discrepancy in the guidelines that we talked about.

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

I also wanted to share this study. I think this was really interesting. This was just in a CID last year in 2023. Again, this is a retrospective study, so different than a randomized trial. But this is propensity matching in a large cohort. This is in the United States. And they looked at remdesivir for immunocompromised patients. Again, similar to the case that we were talking about today.

And when they looked through different variant waves, they actually found that early on, again, remdesivir within 2 days of hospital admission seem to be associated with significant reductions in mortality, both at 14 and 28 days. I think this study is important because often we lament that immunocompromised patients are often left out of different studies. And so I think this is really important.

When you look at the study, they did have to lump a number of immunocompromised patients together. So there might be more work to be done in this space. But thinking again about our case, remdesivir does seem like a good choice.

Immunomodulators

Okay, I'm going to transition to Dr Gandhi.

Dr. Gandhi:

Thanks, Dr Patel. As you put in the outset of the kind of continuum of COVID, inflammation really seems to be driving a lot of the disease when you get to a person like we're caring for—someone with severe shading and critical disease. So we're going to spend some time now talking about the role of immunomodulators.

RECOVERY: Dexamethasone in People with COVID-19

And let's start off with really the study that changed the way we treat COVID overnight, essentially in June 2020. This was the RECOVERY study that was done in people with COVID-19. It was open label. It was randomized. It was done in individuals hospitalized with COVID-19, and they were randomized to get dexamethasone or to not receive dexamethasone.

And what you're seeing here are some of the points that were made before. People on oxygen, people on mechanical ventilation had a substantially lower rate of mortality. So for mechanical ventilation/ECMO was a 36% lower rate of mortality rate ratio of 0.64. And for those just on oxygen, not yet on mechanical ventilation, it was an 18% reduction in mortality. I want to reiterate the point that was made before that in people hospitalized that were not on oxygen, there was actually a trend towards higher mortality.

And certainly during the Delta wave in India and other places, I think some of the challenges were inappropriate use of steroids in people who didn't meet this indication of being severely ill.

Systemic Corticosteroids and 28-Day All-Cause Mortality in Critically Ill Patients With COVID-19

Now, the RECOVERY study would follow soon thereafter by a meta-analysis of a number of different studies that really solidified the evidence base. These are not just the RECOVERY study, but other studies of steroids in people with severe COVID. And really this particular WHO group conglomerated the evidence and there was a strong signal for mortality benefit of the use of steroids in people who, in this instance, had critical illness with COVID-19.

Remdesivir + Dexamethasone vs Dexamethasone Alone for Patients Hospitalized With COVID-19 in US

Now, what has evolved, of course, though, is not just dexamethasone alone. Here are some data that support the use of remdesivir with dexamethasone in people who are hospitalized with COVID-19. Looking now at a combination of antiviral therapy with remdesivir plus dexamethasone vs dexamethasone alone.

Now this is a retrospective study. So it does have the possibility of unmeasured confounders. But at least the way the evidence here is shaping up, it looks like it favors remdesivir plus dexamethasone in this particular patient population. So I think this is why many of the guidelines have evolved to recommending the combination of an antiviral plus immunomodulator here dexamethasone.

Other Immunomodulators

Now we don't stop just with dexamethasone though. People will remember again in 2021 into 2022, intense studies of what we sometimes called augmented immunomodulation. What we mean by that is taking someone who meets an indication for dexamethasone and considering an additional immunomodulator. And the 2 classes that got the most attention are the JAK inhibitors, with drugs like baricitinib and the IL-6 inhibitors with drugs like tocilizumab. So I want to revisit some of the evidence behind these, what we sometimes call second immunomodulators.

RECOVERY and ACTT-2: Baricitinib in Hospitalized Patients With Severe COVID-19

So let's start first with baricitinib. As a reminder, it's a JAK inhibitor, a Janus kinase inhibitor. Here we're showing 2 studies, the ACTT-2 study funded by the NIH and the RECOVERY study done in the UK.

Let's start with ACTT-2. ACTT-2 looked at baricitinib plus remdesivir vs control that was in over 1000 people. What this showed is that there was a reduction or a trend towards a reduction in death when baricitinib was given with remdesivir, and there was also some recovery endpoints.

But the point that I want to make here is ACTT-2 was done at a time where dexamethasone was not yet in widespread use. So really, it's the RECOVERY study that I think informs our decision-making mostly around is the most impactful study around baricitinib. Because what this study is, it looked at baricitinib plus standard of care, where now standard of care did include steroids.

And the important result of RECOVERY for baricitinib is that there was a lower all-cause mortality in the group that got steroids plus baricitinib as compared to the group that just got steroids. And that really kind of changed the game when it came to using baricitinib.

COV-BARRIER and COV-BARRIER-2: Baricitinib in Hospitalized Patients With Severe COVID-19

Now, the RECOVERY study was really supported also by another study called COV-BARRIER and COV-BARRIER-2. These were double blind, placebo-controlled, randomized controlled studies. Let's start with COV-BARRIER. This was done in people who had elevated inflammatory markers. It was a randomized study of baricitinib vs placebo.

In COV-BARRIER, about 80% of people were on steroids. The important point about COV-BARRIER is the mortality signal. So if you look and zero in on the mortality signal, there was an 8% mortality in the individuals who got baricitinib, mostly with steroids vs 13% in the group that got placebo. So this was a really substantial reduction in mortality.

COV-BARRIER-2 was done in an even sicker group of people than in COV-BARRIER. And COV-BARRIER-2 was done in people on invasive mechanical ventilation or ECMO. So really the sickest of the sick. 86% of them were on steroids. This was a small study compared to COV-BARRIER. But here too, you see lower mortality in the baricitinib group versus the group that got placebo. And again, majority of people getting steroids.

RECOVERY: Tocilizumab in People With COVID-19

Let's shift gears now from JAK inhibition with baricitinib to tocilizumab. This is an interleukin-6 inhibitor. Here I want to again highlight some data from RECOVERY from the UK, open-label, randomized study. People hospitalized with COVID, all of whom had severe COVID. They had oxygen saturations less than 92% on room air.

And in this instance, they had systemic inflammation. And what RECOVERY defined as systemic inflammation is having a CRP of greater than 75 mg/L.

And the bottom line here is that the tocilizumab group did better than the usual care group, and the usual care group, 82% of people were getting steroids. So again, evidence supporting the use of this IL-6.

REMAP-CAP: Enrollment at 113 Sites in 6 Countries

REMAP-CAP was also done around the same time. Multinational study with multiple sites involved. And here the comparator was usual care. And what they were looking at were 2 different IL-6 inhibitors. Tocilizumab, the one that we use mostly in the US and one called sarilumab. And so this was a randomized trial looking at these different interventions. I'm going to leave out the anakinra interferon for the purpose of time.

REMAP-CAP: Tocilizumab and Sarilumab

And here are the results are shown on the next slide. And this complicated series of graphs is largely just pointing to the fact that there was a survival benefit in the group that got the IL-6 inhibitor, tocilizumab, or in this instance, sarilumab as compared to usual care.

The reason why we mostly favor tocilizumab is there are even more data with tocilizumab than there are with sarilumab. If you don't have access to tocilizumab, then sarilumab is a good choice.

So I'm going to now bring it back to our faculty. And we're going to take what we've learned in terms of the data for antivirals, remdesivir in particular, as well as these immune modulators. And maybe I'll start by asking, Dr Patel, how would you take what we know now and how would you treat this person who has some immunocompromise, not currently on rituximab or on EPOCH chemotherapy, but has pretty rapid progression over the course of 2 days now on 6 liters and may be going in the wrong direction. What would you do?

Dr. Patel:

Yeah, I think there's really good evidence early as we've talked about for remdesivir. So I think that's a given. Depending on their oxygenation, steroids, you know, I think are definitely a given.

And then, you know, one thing that we found helpful is some scores for inflammation. So we use a score called the CHADS2 score. And you can kind of plug in some inflammatory markers and that can help you decide on the second immunomodulator whether you want to use something like baricitinib. And I think that's kind of how I would think about it in this case.

Dr. Gandhi:

And Dr Cantrill, you mentioned that you are a big proponent of doing things as quickly as possible rather than waiting unnecessarily. How would you engage your colleagues around this patient? How would you actually implement getting some of these drugs started?

Dr. Cantrill:

It's really a matter of first deciding what the team wants to do, and then it's the logistics of getting the stuff if it has to come from pharmacy, and sometimes you have to ride people a little bit. And that's my job. And you know, and talk with the nursing staff and just make sure it happens because, you know, time is critical in these folks.

And I would really worry about this lady because she shows evidence of going downhill pretty rapidly, and I wonder if she isn't going to end up being intubated in the ED, which I would rather not do. I'd rather use other less invasive ventilatory techniques, but sometimes that's what's going to happen.

Dr. Gandhi:

You know, one thing we might want to hearken back to is even if this person ended up getting intubated in the ED, this discussion around whether remdesivir suddenly kind of magically loses its potency as soon as you get intubated. And I think biologically, it makes sense to me that someone who's early on as Dr Patel said.

And in this instance, who's immunocompromised, where we have good evidence that her own immune system is less likely to be able to contain the virus, that even if she were to be intubated in the emergency department, now she's—you know, we're now extrapolating evidence as opposed to having firm evidence. I think I would give the immunomodulator, but let's start remdesivir on and that would be the rationale is, you know, we're never going to have—and this is true of all of medicine—we're never going to have every single bit of data for every single patient. That's where the clinical judgment really comes in.

Dr. Cantrill:

Yeah, Raj, I agree with that. I mean, especially the history we have is that this has been going on for only 2 days. So her viral replication is probably still quite active. And this is our chance to attenuate that with remdesivir.

Dr. Gandhi:

That is a nice segue, I think, into some of the unknown things that we do need to - we know a lot, but there's things that we don't know. And so maybe we'll spend a minute and talk about that as well. But before let's bring back the guidelines and really see how they apply to this patient. We talked about that this person was requiring supplemental oxygen, does seem to be getting worse. So I think dexamethasone for sure.

I think we heard good arguments for also adding remdesivir. And then with elevated markers of inflammation, I think baricitinib IDSA would endorse or tocilizumab. And here it largely would depend on what institutional capacity is, what you have most readily at hand, as well as some of the issues around oral therapy vs intravenous therapy.

Patient Case

So our patient, again, is a 45-year-old woman, had mediastinal lymphoma as we heard about, has gotten rituximab about a year ago along with chemotherapy. She's presenting with severe disease, getting ill quickly and had prior immunity, but several years ago in the form of vaccination three years ago and COVID-19 2 years ago.

And in terms of the choices that we gave you at the outset, please go ahead and vote. And let's see how the discussion has influenced your vote here.

Posttest 1: Rationale

The current guidelines would recommend remdesivir and dexamethasone in hospitalized people, persons like this and then either baricitinib or tocilizumab.

So I know we all lived through the kind of the rapid evolution of where we got to now. But - but maybe I'll ask Dr Patel, what would you most like to know in terms of how we could make our therapies better? What are some of the unknowns that we really—or what are the gaps related to patient care that that we really need to fill in, in the years to come?

Dr. Patel:

Yeah, that's such a good question. And you know, I feel like we had a brief moment where some of those gaps were filled for a while. We had some preventive therapy for, you know, patients who are immune-compromised, but those are no longer available. And so I think we've seen so much in the treatment of COVID, and we've seen a lot actually, in the trials that we discussed.

I think there was some really great early work done flexibility within our government and internationally that helped us learn a lot when we think about, you know, what happened and what has happened. So I think that there's a lot of lessons learned.

From the research standpoint, I think, you know, the more recent work that has been looking at special populations is still really important and I think can help us understand, you know, more of these I said shadations before, but I mean, gradations of like trying to understand for this, you know, potentially for a BMT patient, you know, is there something that's better than potentially for a solid organ transplant patient? So that's something that I'd be thinking about.

Dr. Gandhi:

I would like you to coin the word shadation. I think that's a keeper. Dr Cantrill, what do you think an ED physician or clinician in the future really needs to know that they don't know today?

Dr. Cantrill:

Oh, gosh. I think if we could understand better what factors put these patients at greater risk for decompensation, so I can anticipate where I'm going to have to go with the patient. That, to me would be very, very helpful.

Dr. Gandhi:

Yeah. We'll say the RECOVERY studies did us a great favor because they - they transformed how we treat COVID-19. But of course the RECOVERY studies were done almost in the cardiology mode, where they did tens of thousands of people, and therefore they didn't and couldn't realistically do the kind of biomarker data that, honestly, the NIH is particularly good at. So I would love to know, are there biomarkers that could tell me which patients to use a particular immunomodulator in?

If I have someone on 1 liter of oxygen, you know, it's not like RECOVERY studied people to that level of detail. And so maybe they should just get remdesivir and just be watched very, very carefully before getting dexamethasone.

So now I don't know that to be true. And I think the default is to give dexamethasone. But maybe we could really refine our understanding of exactly how to intervene. And that's where kind of the translational work coupled with the big clinical trials can make advances.

And then the last thing I will say is that immunosuppressed individual. We didn't highlight this, but I'll mention it now. A lot of the data that was done with immunomodulators, that came from immunomodulatory trials didn't study the most immunocompromised people. And that's where I think we do need either new trials or analyses of observational data to really understand if you're heavily immunosuppressed, should we still have the same approach, or should we have a more customized approach to the gradations really matter.

Immunomodulators: Additional Considerations

So a few additional considerations with immunomodulators. Do avoid or use with very great caution in people who have other infections like bacterial, fungal or non-SARS-CoV-2 viral infections. In the early days of COVID, we used to worry a lot about co-infections or super infections with bacterial pathogens. That's not common, but it does occasionally happen. So be careful if they have a pneumonia—a bacterial pneumonia on top of their COVID.

And then do remember, of course, that prolonged immunomodulatory therapy can lead to reactivation of latent infections, things like hepatitis B, herpes viruses, if they're from the right part of the world. And that includes the US, Southern US as strongyloidiasis and tuberculosis are used with caution in people who are heavily immunosuppressed or at high risk for gastrointestinal perforation.

And then just a reminder one more time that people from warm temperate regions should be screened and treated to prevent strongyloidiasis, something that's easily prevented with treatment.

Key Take-home Points

So a couple of key take-home points. The treatment of COVID-19 in hospitalized patients depends both on the host and on the severity of the disease. The two-part series that we have really illustrates that.

Remdesivir is most beneficial early in disease, before patients are critically ill, and in those who are immunocompromised. And in people who develop severe COVID-19 or critical COVID-19 and require oxygen, immunomodulators are recommended. And we've gone through some of the specifics.