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Evidence and Guidelines for COVID-19 In-Hospital Management: Putting It All Together

Announcer Open:
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Dr. Mukherjee:
Hi, everyone. Thank you for joining our session here. My name is Vikram Mukherjee. I'm a Pulmonary Critical Care Attending Physician at the NYU School of Medicine, where I serve as the Director of the Medical Intensive Care Unit, and I'm joined here by Cameron Smith. Cam?

Ms. Smith:
Hi, I'm Cameron Smith, Physician Assistant at Bellevue Hospital, Lead APP in the medical ICU.

Dr. Mukherjee:
And Cam and I have worked with our team here through the throes of the pandemic, and have seen COVID for the last almost 3 years now, through the various surges that our Bellevue Hospital has gone through.

Ms. Smith:
Our learning objectives for today, we're going to distinguish amongst the criteria for assessing disease severity in hospitalized patients with COVID, compose guideline-supported treatment plans for hospitalized patients with COVID, analyze clinical trial data-supported therapies for hospitalized patients.

Dr. Mukherjee:
So we'll start with an overview on the current state of the union on where we are with COVID-19 hospitalizations. And, you know, what we want to emphasize on this slide is even though we're close to 3 years into the pandemic, COVID is still very topical to hospitalizations. In fact, this winter, we're looking at the triple threat of COVID admissions, influenza admissions, and RSV surges. As you see in this slide, there have been various surges of COVID-19 hospitalizations and as recently as this month and last month, we're still way higher than where we were back in summer of this year. So again, this is a timely reminder that we are still very much in the middle of a pandemic. And it's still important remember to get vaccinated, to get the non-pharmaceutical interventions into place as we look towards what happens with the next few months and this winter.

I want to emphasize again on the vaccination question, this is a beautiful slide which shows the difference in hospitalizations between patients who are vaccinated, and those are not vaccinated. The line in the blue are hospitalizations on people who are fully vaccinated. And the one in green shows rates per 100,000 population in patients who are not vaccinated. And as you can see here, there's a big splay and it continues to emphasize the protective effect against severe COVID-19 manifestations by timely, reliable the vaccine access.

Ms. Smith:
Alright, so the slide is showing us that there are several comorbidities related with risk factors for severe COVID. The main one is patients who are over 60 years of age, we also see this in flu, that the older the patients are, the more at risk they are. Additional risk

factors include COPD, if you're overweight or obese, if you have CKD, any kind of cardiovascular disease, and then several others, including smoking, immunosuppression, diabetes, and cancer.

Dr. Mukherjee:
And you know, one of the things that we would find very useful in the hospital is to kind of predict which patients will do just fine on the floors, versus which patients will need higher levels of care, a step-down unit or an ICU, or even worse, a ventilator, or ECMO. And this is a very well validated tool that could be used in a real-world scenario where you take patient demographics and have a prediction model of how likely the patient is to end up with severe COVID, requiring ICU admission. It takes into account underlying comorbidities, of course, age, gender, whether the patient is coming from a nursing home, underlying race, and whether the patient has respiratory or gastrointestinal symptoms. I do want to emphasize that this was before - this was validated before the vaccines took over, so please also factor in that patients who are vaccinated, end up doing much better in terms of risk of severe illness, do factor that in as you make these risks predictions. Cam?

Ms. Smith:
Alright. And then of course, you know, we know the main symptoms in COVID involve the lungs, but there are several extrapulmonary manifestations of this. The ones that we see the most, especially with the first wave of the pandemic, are DVTs, pulmonary embolism, and then AKI, so the damage to the kidneys during this time, but you can see really, every single system can be affected by COVID.

Dr. Mukherjee:
And to Cam's point, I do want to echo that, you know, we still are, even though it's been 3 years, and close to 3 years into the pandemic, we're still understanding the mechanisms of disease. And you know, where we have some understanding of why patients are hypercoagulable, and through venous and arterial clots, the cardiac manifestations, whether they're an autoimmune pathway versus direct vital infiltration, the endocrinopathies, we're still very early in this disease process to understand exactly how this works, and how to stop it from occurring. Cam?

Ms. Smith:
Alright, this is a review of the NIH guidelines for the severity spectrum. Most of what we see in the ICU, of course, falls within the severe illness to critical illness category. But you can see pretty much we know people that have been asymptomatic or presymptomatic, they are not showing any symptoms, but they are positive. And then with a mild illness, you can have generalized symptoms. Moderate illness, you know, now our SpO2 is much lower; with severe illness, it is even lower than that. You can see the classification criteria, the PaO2 and FiO2 are below 300 on room air, and then of course, you can have increased respirations and then lung infiltrates, the ground-glass opacities, which we are used to seeing on x-ray. And then of course with critical illness, this is where we get into the respiratory failure, septic shock, and multiorgan dysfunction. And the important thing to take away is that patients in any category, whether you have had zero symptoms or been intubated, are at risk for long COVID.

Dr. Mukherjee:
Thanks Cameron. I do want to emphasize what Cam mentioned, long COVID or in a post-acute sequela of COVID. Again, this is still - the jury's still out there on how/why this occurs, but as many of you know, it's debilitating in the long run. It's up to 20% of patients with acute COVID, even the mild or presymptomatic COVID can develop long COVID. And this manifests as neurocognitive dysfunction, it's not so much of a respiratory illness, but more so of a nervous system illness with neurocognitive dysfunction with psychiatric illness long out from the acute phase of COVID.

There's some early data showing that it's because of viral reservoirs of COVID, of SARS-CoV-2 persisting in astrocytes and nerve cells, but how to stop it, and what consequences this has on the workforce, on economy per se, is still up to - is still very early to comment on that. But it's something that all of us have our eyes on and a lot of funding coming along to study the pathogenesis and how to stop long COVID or post-acute sequelae of acute COVID.

Now that we have overviewed or, you know, reviewed the basic pathophysiology and how a patient progresses from an early infection from all the way from asymptomatic or presymptomatic disease, and sometimes all the way to severe or critical illness, it's important for us to also review the pathophysiology behind this progression of clinical disease. That's important one is because it helps us predict what happens next and also be - help us target countermeasures and therapeutics to a particular phase of the infection, of the infectious process.

So what's been well described over the last couple of years is that a SARS-CoV-2 infection has kind of a triphasic response. There's an early infection, which is marked by profound SARS-CoV-2 replication. The next phase is a pulmonary phase where you have essentially a viral pneumonia, there's some infiltration of the virus into the pulmonary parenchyma. But the third phase is important to remember that the third phase is essentially a dysregulated host immune response. And it's essentially a consequence of that which leads the patient to get into a critical illness often with acute respiratory distress syndrome, and so on. So it's really important to remember that

viral replication at the early infection, which then goes into some viral pneumonias, but then the last or the third phase is the hyperinflammatory phase, which is because of a dysregulated host immune system response.

The reason this is important to know is because the clinical signs often differ. In the early infection, it's a bit of a fever, a dry cough for the presymptomatic/asymptomatic phase. The pulmonary phase is when it starts getting a little serious, you have hypoxia, you have ground-glass opacities on the chest CT, you may have some liver dysfunction. And lastly, the ICU patients, the patients who unfortunately don't have great outcomes, are the ones who have a hyperinflammatory response, and these patients manifest by acute respiratory distress syndrome, needing mechanical ventilation, sometimes ECMO, elevated inflammatory markers, myocarditis, and so on.

And you know, now that we understand the 3 phases, we can target our countermeasures to each of these 3 phases. So if the patient presents early, you would use antivirals, remdesivir or others, to be able to target and stop viral replication. If they present late in the course of the disease, immunomodulators, such as steroids, are, you know, we'll come to more of that in the later half of this talk. But immunomodulation to dampen the host inflammatory response would be the way to go to avoid the badness of ARDS and cardiac failure.

Now that we have an understanding of the pathophysiology and the disease severity classifications, we'll describe a couple of case studies. These are real-world scenarios that have evolved from the Bellevue ICU here. And we feel that, you know, going through these case studies together, reviewing the data behind them, and the management of them will be a nice reminder on the evidence-based management that lends itself to good clinical practice at the bedside.

So with that in mind, I'm going to hand it over to Cam to take us through the first case. Thanks, Cam.

Ms. Smith:
So this particular one is a 65-year-old male, a past medical history of hypertension, hyperlipidemia, and diabetes type 2. So he presented to us in the ICU from the ED after 6 days of dyspnea and increased work of breathing. His vitals had a slight fever, slightly elevated heart rate, elevated respiratory rate, and we know he has hypertension at baseline, so that is not unusual. The big thing to look at is that he had an Sp02 to 86% on room air. That is significantly low. Your normal ranges are supposed to be between 92 and 100 typically. Of course, with all of these patients, we get a chest x-ray right away and review it. These showed diffuse ground-glass opacities, which is classic for COVID-19. His rapid test came back positive. Unfortunately, he was unvaccinated. This was during the first wave of the pandemic, and we did not have vaccinations at this time. Labs were notable for a AVG of 7.2, so a bit of respiratory acidosis here. White blood cells were elevated. And then elevated biomarkers. At that point, we were tracking LDH, D-dimer including a D-dimer of 5000. We were checking IL-6, several others. The patient was quickly placed on high-flow nasal cannula at the max settings we could put him on, and he did have improvement to his SpO2, but only to 90%. Unfortunately, he became increasingly more tachypneic, use of accessory muscles, so now in respiratory distress. And this patient was a triaged to us in the medical ICU for this increased oxygen requirement.

To give you some background information on NIH guidelines for therapeutic management of these patients with severe COVID, if there weren't minimal oxygen, you can use remdesivir alone. Elevated 02, add dexamethasone, or if remdesivir is not available at your hospital, you can use dexamethasone alone. And then despite what you are already doing, if they still have increasing oxygen requirements and they're having systemic inflammation, then you can add the baricitinib or tocilizumab to the dexamethasone. So the answer is remdesivir and dexamethasone. Remdesivir, simply because that was our first line and FDA approved supportive measure. And then dexamethasone because his oxygen requirement was below 94%, despite giving increased oxygen support.

Alright, and then this is a review of the WHO guidelines supportive management for COVID-19. Of course, first things you're going to do for a patient who has a positive test and appears like they may be in distress or need to be monitored closely, you're going to want to put on a pulse oximeter to measure their Sp02, make sure that the Sp02 stays above 92 to 94%, give them supplemental oxygen should they need it, monitor for clinical deterioration because these patients can deteriorate very, very quickly. And then be very cautious with fluid management in these patients, unless they have tissue or hypoperfusion with a super high lactate, if you give them a significant amount of fluid, that fluid is just going to cause their respiratory distress to worsen.

Dr. Mukherjee:
Thanks, Cam. That's a really nice description on what's essentially a very classic case of a patient with COVID who presented to the ICU. I do want to emphasize a couple of things, you know, echoing Cam's thoughts about supportive management. In this day and age when we see COVID in the ICU, we should also remember to check for flu, check for RSV. It's a particularly bad influenza season this year, so please make sure differentials are still very broad. And also remember that, you know, a lot of patients in the ICU with COVID still have or are at higher risk for venous thromboembolism for PEs and DVTs. In fact, as Italian data showing that 2 out of 3 patients with COVID in the ICU will have venous thromboembolism so keep the differentials broad. Even though COVID might be the primary

driver of the critical illness, have some point of care ultrasound done, have some markers to check whether there's something else underlying the overwhelming COVID infection.

I'll take case 2. This is again a real-world scenario from the initial pre-vaccination surges In New York. We have 32-year-old female, 25 weeks of gestation, gravida 1, para 0, presenting to our ICU as transfer for an ECMO after testing positive for COVID-19. Again, this was, as Cam mentioned in the pre - in the first phase, so vaccines weren't available. Then she deteriorated clinically during the ICU, still requiring invasive mechanical ventilation. And as you know, this is the one patient that will keep us awake at night, the young otherwise healthy woman who is pregnant and this would be our highest priority, which is why she came to Bellevue for possible ECMO. Very rocky course. So despite an aggressive conventional maneuvers that have been time tested for COVID for 16:39 ARDS, that has lung protection, PEEP titration, recruitment, she still remained very hypoxic. And as we all know, that has significant consequences, not just on the mother but also on the fetus. And the decision to place the patient on venovenous ECMO was taken. And I'm sure all of you know about the venovenous ECMO, but briefly, it takes blood out of the veins from the internal jugular of the femoral, passes the deoxygenated blood through a pump, and oxygenator and a carbon dioxide removal machine, and then pumps the blood back into the right side of the heart, basically taking over the entire function of the lungs. So this patient was placed on VV ECMO, she was cannulated. And after a 2-week run of ECMO, she was improved. She improved enough to be decannulated. And by God's grace, her pregnancy was preserved. Over the next few months, she had a uneventful peripartum period and delivered healthy baby around 2 months or 3 months after this ICU admission. This was one of the few success stories we had during the first wave. And this is very close to our heart, because she got the care that could not have been delivered in many other parts of New York City during those services.

Essentially, this is a short story, and we'll review the data behind this. Essentially the NIH guidelines, the therapeutic management for hospitalized patients with critical COVID-19, essentially, we tried to break it up into supportive care and countermeasures. We'll walk through the slide together. On the left here is the patient requires high-flow oxygen or non-invasive ventilation, essentially a CPAP or BiPAP. You should start thinking about dexamethasone or baricitinib, or dexamethasone plus toci. If you don't have any of those other options, dexamethasone alone should be sufficient. And if you have an immunocompromised patient, you should be thinking of adding remdesivir, simply because viral replication happens for a longer period if you have an underlying immunocompromised disease.

In a patient who requires invasive mechanical ventilation or ECMO, such as our patient, the guidelines are very clear, dexamethasone plus bari, or dexamethasone plus toci, as well. And you should be studying these much earlier before they end up on ECMO. The correct answer is dexamethasone plus baricitinib. This is in line with current NIH guidelines and has a couple of really good trials which we'll review in a minute to back this route of management. Just reviewing the WHO guidelines again, supportive management is very essential in patients with critical COVID-19, acute hypoxic respiratory failure. We usually start with nasal cannula, quickly upscale to high-flow nasal cannula. BiPAP has some contradictory data to it, so if a patient isn't doing well on high-flow nasal cannula, many of us go directly to invasive mechanical ventilation. As the patient develops acute respiratory distress syndrome, or ARDS, we use supportive management such as lung protective strategies, inhaled nitric oxide, PEEP strategies, recruitment, and so on. And then ECMO is always a tool, of course, we only use it in patients who have good prognostic outcomes. So most patients who end up on ECMO are younger healthy patients will have single-organ dysfunction, and are presenting fairly early in the disease.

And as Cam mentioned, conservative fluid management, we try not to flood the lungs or the tissues with unnecessary fluid. So a very prudent conservative fluid management is what is usually advised in an ICU setting.

Cam, back to you.

Ms. Smith:
Alright, this is a slide, and I know this has been mentioned in several studies, and of course, we talk about it in the ICU all the time, but as Vikram just mentioned, we don't want to have fluid overload in our patients, it leads to increased mortality. And so, we always say a dry lung is a happy lung.

Okay, so, ventilation management can be very complicated. But for COVID, we have a few guidelines that the WHO has set up and we've also found very helpful in the ICU setting. The first is the tidal volume. So we want to give these patients lung protective volumes, which means they are somewhere between 4 and 8 mL/kg of their predicted body weight. We want to keep their inspiratory pressures low as well. Their PEEP can be high. I've seen PEEP as high as 20 actually in some of our much more obese patients. And typically, your PEEP is going to be at 5. But again, with COVID, you could have it quite higher. And that's mostly because these lungs become so stiff, that you need extra pressure to open up and recruit your alveoli for better oxygenation. The Fi02, most of these patients we put on 100% Fi02 at first, and then we get an ABG, an arterial blood gas, and we wean that as able.

And then I think this is pretty common sense, but you definitely want to avoid vent disconnection. Sometimes thinking, you know, if a

patient is in distress, despite being on a ventilator, that you might disconnect them and, you know, bag them to try to re-recruit, but there's actually a very high incidence of if the ventilator is disconnected, that these alveoli just close up. And then it's very, very difficult to get them open again. Some patients that we've seen disconnected from ventilators only temporarily may take 30 minutes to an hour just to re-recruit their alveoli for proper blood gas exchange.

Dr. Mukherjee:
Thanks, Cam. And that's a really important point. You know, I mean, most of our patients with severe ARDS will fit criteria for prone positioning, and you want to be doubly sure that someone's keeping a very, very careful eye on their airway and the vent or EG tube doesn't get dislodged or disconnected. As you reposition the patient on a prone position, we've, as Cam was mentioning, it takes a long time, and you can risk for hypoxia if those ventilators or EG tubes get misarranged.

Thanks, Cam, back to you.

Ms. Smith:
Thanks, Vikram. And speaking of the proning, you know, I really have to, you know, commend our hospital in particular, and I know the other ones around who all had proning teams, which were very instrumental in helping to prone all of our patients to help re recruit alveoli during the first wave and onward. It was a very helpful intervention.

This slide is giving guidelines from the WHO on trying to prevent ventilator-associated complications. With all patients that are ventilated, you want to do a daily spontaneous breathing trial, and a spontaneous awakening trial, as well as evaluate their RASS score, which is the Richmond Agitation Sedation Scale. So even though these patients may need the ventilator, you still want to give them every chance to come off of it if able.

Another thing that we see commonly in patients who are ventilated for a long period of time is that they acquire a ventilated - a ventilator-associated pneumonia. And so to kind of help combat this, we put their head of bed up to 30 to 45% and then they have daily tubing exchange to prevent that.

Something else we want to prevent in these patients are thromboembolic events, this could be a DVT, a PE, acute coronary. And so we will typically give these patients prophylactic. And sometimes if they qualify for it, therapeutic doses of anticoagulation.

We also want to avoid pressure ulcers in these patients. So whereas in the ICU, we have a lot more attention to patients, we can turn them more frequently, preferably every 2 hours, it is important to avoid these pressure ulcers if possible, because this can lead to just another major source of infection. We've seen a lot of sacral decubitus ulcers that just really wreak havoc on these patients. Stress ulcers, also a thing to think about.

For GI bleeds, if your patient does not receive 2 feeds within an allotted period of time, then you probably want to start them on an H2 blocker or a PPI.

We also want to avoid line-related bacteremia. And so it's really important whenever putting in lines, especially central lines in these patients, because they require several medications at once, that are maybe not compatible on a peripheral IV, that we do everything sterilely. And we also want to minimize the time that they're in. So in your hospital, it may be different. In our hospital, 7 days is the max amount of time that you should have in a central line. And that will need to be exchanged to prevent line-related infection.

We also want to be good antimicrobial stewards, and not use antibiotics and antifungals so cavalierly. These COVID patients, this is a virus, and so if they don't have a bacterial infection, they don't need antibacterials. So if they don't have a fungal infection, they don't need antifungals. This is something really important that I want to hit home with.

And of course, we always have to review the drug-related interactions with a lot of the medications we give these patients and the side effects. You know, a lot of patients who have been under sedation for a long period of time, and who have been ventilated for a long period of time, will have an ICU-related delirium. And so we want to be very cognizant of that, and kind of gently transition them into wakefulness as possible.

This slide reviews the NIH and WHO guidelines of patients with septic shock. I think, if you're in an ICU setting, if you're in a medical setting, you should really know what shock is already. But just to review, we want to give fluids, but be very mindful that giving too much can really overwhelm the patients and flood their lungs. So again, a dry lung is a happy lung. And if they need consistent pressors, if they need blood pressure support, then putting in an arterial line will help not only monitor constantly their blood pressure so that you can titrate these medications appropriately, but we can also obtain serial ABGs to see how the patient is doing on a ventilator. For our vasopressor adults, our first line is typically norepinephrine. And you really can consider dobutamine if the patient has poor perfusion and has cardiac dysfunction at baseline.

Dr. Mukherjee:
Thanks, Cam. And now that we have a brief understanding of the supportive care that the ICU patient with COVID-19 deserves, shifting gears a little bit to the countermeasures that are out there and what we can use in conjunction with the supportive care that Cam just mentioned to improve outcomes in the ICU. So what we'll go over for the next few minutes is evidence-based medications for hospital management of COVID-19. And we'll review the 4 main categories of countermeasures, essentially antivirals, anti-inflammatories, IL-6 inhibitors, and JAK inhibitors. Each of them have a role to play in the management, they're not exclusive to each other. And as you'll see in the evidence that we'll review, because they work in parallel pathways, they usually are used in conjunction with each other.

This slide shows the anti-inflammatory immunomodulatory therapies for COVID-19. Essentially, as you all know, there's the SARS-CoV-2 virus, which has the spike proteins on its surface and attaches to the - by the ACE2 receptors to the cell surfaces. As a consequence to that, there is the host immune system response and anti-spike antibodies are often mounted. Along with that there are proinflammatory cytokines, macrophage monocyte recruitment, which ends up leading to pulmonary edema, thromboembolism, and pulmonary fibrosis. Again, part of the countermeasures focus on viral replication and making sure that the SARS-CoV-2 replication itself is diminished, and part of it is going to be immunomodulation so that the dysregulated host immune system is not as damaging as it possibly can be.

So in that line, we'll start with the 4 main categories. The first one is antivirals. So, the first antiviral we'll discuss is a combination pill of nirmatrelvir and ritonavir. And essentially, the indication for this is for 2 patients – 2 categories of patients, nonhospitalized patients with mild to moderate COVID-19 at high risk for disease progression, such as older patients, immunocompromised patients, and so on, or hospitalized patients initially admitted with a diagnosis other than COVID, for example, trauma, provided that they have mild to moderate COVID-19 and are at high risk for severe disease progression. The mechanism, this is not a new drug, it's been there for a while. The mechanism of action, it's a combination. Nirmatrelvir is a protease inhibitor, and ritonavir inhibits metabolism of nirmatrelvir, so it's adjunct to that. Of note, it is not recommended for patients with severe hepatic impairment. It's otherwise a fairly common drug to use. We've used it a lot, not only in the inpatient setting, but also in the outpatient setting. And the side effect profile usually is fairly safe. The dosing, it's a 5-day course, initial treatment as soon as possible within 5 days of onset. Remember, it's an antiviral, so the quicker you have it on board, the less the viral replication is during the first phase of COVID illness. Most academic societies and professional organizations have used this in their guidelines to prevent severe illness.

Cam, over to you for the next antiviral, please?

Ms. Smith:
Alright, thanks, Vikram. The next antiviral we're going to talk about is remdesivir. So the indication, it's FDA approved for patients who are hospitalized with COVID, or even patients who are not hospitalized with mild to moderate COVID-19 who are at high risk progression to severe disease. So you know, we were talking about patients in earlier slides that have multiple comorbidities, and so this is the population we're talking about here. Mechanism, it's an nucleoside analogue of ATP, which we know is really important for energy in the body. And it essentially inhibits the RNA polymerase in the COVID virus. And now it's not recommended typically for patients who have decreased kidney function, so your GFR, if it's below 30, you're probably not going to use this on your ESRD patients or chronic kidney disease patients who are in the later stages. It is contraindicated if you've had a hypersensitivity reaction to remdesivir before or any components in it, and you want to discontinue this medication if there's a clinically significant hypersensitivity reaction. You want to initiate this treatment as soon as possible after the diagnosis of COVID. And then you can see the administrative doses, we are going to give 200 mg IV first on first day, and then you're going to follow that by fo4ur days, for a total of a 5-day course. Sometimes you can extend these courses. I know earlier in the pandemic, we extended the courses up to 7 to 10 days. It really just depends on the patient. And, you know, we work really closely with our critical care pharmacist on this one, they have great recommendations.

Dr. Mukherjee:
Thanks, Cam. And just to echo what Cam is saying, remdesivir is still the first FDA approved countermeasure for COVID-19. And we have a lot of trust in this in the right patient population. Of note, it is an IV formulation, the medication we mentioned earlier, can be given oral. So outpatient therapy can be a logistically challenging mechanism. But it is something that we have used a lot both in the outpatient and inpatient setting. The data behind this is robust, Cam.

Ms. Smith:
This is the ACCT-1 study showing the time to recovery between remdesivir versus a placebo. Patients were in 2 categories, ones who did not require supplemental oxygen, and ones that did. And the takeaway from this is that there was improvement in recovery time, seen purely in patients who needed oxygen support. But no significant difference seen in patients who did not require supplemental oxygen.

And then this is this SIMPLE-Severe study showing the efficacy of remdesivir in either giving a 5-day course versus a 10-day course.

And the takeaway from this is that while there was significant clinical improvement with these patients giving remdesivir period, there was not a statistically signal difference in giving a 5-day course versus a 10-day course.

Vikram, what do you think about the SIMPLE-Moderate study with patients with moderate illness?

Dr. Mukherjee:
Very similar to what was shown in the SIMPLE-Severe study, the SIMPLE-Moderate study didn't back 10-day course of remdesivir. There were no hard clinical improvement in patients who received a longer course, 10 days versus a 5-day course of remdesivir.

Moving along from antivirals to immunomodulators, the game changer here honestly, is dexamethasone. And, Cam, back to you about the role that dexamethasone plays in our critically ill patients.

Ms. Smith:
Alright, thanks Vikram. So dexamethasone, very widely used throughout different illnesses, but for the NIH guidelines, the indication is patients who are requiring supplemental oxygen. So we've given this multiple, multiple times throughout the different COVID waves. It suppresses the migration of neutrophils, decreases lymphocyte colony proliferation, not recommended for hospitalized patients who don't require supplemental oxygen, that's just not needed. And then it's contraindicated in patients with systemic fungal infections. So if you think of dexamethasone, the side effects, it's going to increase your blood sugars. Bacteria love to feed on sugar, and so it's just going to exacerbate any kind of bacterial infections, but especially fungal infections. It can cause elevated blood pressure, heart problems, it can cause adrenocortical insufficiency, increased susceptibility to infection, which we've discussed, possible cataracts and glaucoma, possible optic nerve damage. You know, you can see some of this kind of tracks with someone who has uncontrolled diabetes as well. And then the administration typically will give 6 mg IV once daily, but we will consider more if they require a higher level of respiratory support. I think we've done as high as, and Vikram, correct me if I'm wrong, but I want to say we've done as high as 20 in some patients, and then done 20 for 5 days, 10 for 5 days, and done a taper for patients who require even more oxygen.

Dr. Mukherjee:
You're right, Cam. And that stems from the pre-COVID DEXA-ARDS study where the trial dose was 20 mg IV followed by a quick taper. We are very cognizant that you know, because of the hyperimmune phase of COVID illness, dexamethasone has a role to play, but the side effect profile can be pretty expansive as well, like Cam was mentioning. You know, hypertension, hyperglycemia, but also in a setting of paralytics and neuromuscular blockade, you have significant critical care myopathy. So we do start high or higher when the patient has critical illness sometimes, but also make sure that we taper it off in a very timely manner.

Thanks, Cam, back to you.

Ms. Smith:
Alright, so this is the RECOVERY trial. And so, giving dexamethasone was actually associated with lower mortality among patients who were mechanically ventilated, or receiving just oxygen alone, but not for those receiving no baseline respiratory support. So, you know, just expanding on what we talked about in a bullet-point on the last slide, which is, if someone doesn't need supplemental oxygen, they don't need dexamethasone.

Dr. Mukherjee:
Thanks, Cam. And I do want to emphasize that, you know, because the reason why that is not statistically significant, but it's almost there, the confidence intervals on this graph, as you can see are 0.91 to 1.55. And the probable reason why that's happening is because in the setting of steroids, there can be uncontrolled viral replication, because your immune system isn't working as good. And that can lead to poor outcomes. We've seen in other Coronaviruses such as MERS and SARS-CoV-1, that using steroids early in the disease in nonhypoxic patients can have worse outcomes. So be very careful that dex and other steroids should be used only when the patient needs respiratory support, is hypoxic on the vent, on ECMO, and so on.

The next big category of immunomodulators working with the host immune system, are 2 numbers, tocilizumab and sarilumab. We'll quickly review the data behind them. Essentially tocilizumab, or toci as we call it, is an IL-6 inhibitor. It can be used for hospitalized patients who are receiving steroids and hypoxic who are critically ill requiring noninvasive, invasive mechanical ventilation, or ECMO. So it's an adjunct to systemic corticosteroids in critically ill patients. The mechanism, as you mentioned, it binds specifically to both soluble and membrane bound IL-6 receptors, thereby inhibiting the inflammatory cascade that is so prevalent in critically ill patients. It's not recommended in patients who have liver disease, liver failure, and of course contraindicated in patients who have hypersensitivity reactions. The immune system is so heavily dampened by a double immunomodulators, dex and toci, you know, as we just mentioned, that you should be keeping your radar up for secondary fungal infections, secondary bacterial infections.

There are 2 big trials on tocilizumab in the critical care setting, the first one is EMPACTA, which compared tocilizumab versus placebo in patients with COVID-19 pneumonia. Again, really well designed, international randomized, double-blinded, placebo-controlled, phase 3

trial, and essentially looked at patients who are hospitalized with COVID-19 pneumonia, and divided them into 2 arms, well-matched arms, tocilizumab plus standard of care, versus placebo plus standard of care, with the primary endpoint being deterioration of these patients. So cumulative proportion of participants requiring invasive mechanical ventilation, or dying within 28 days of enrollment. The good news is that primary endpoint was met. Patients who receive tocilizumab compared to placebo, had a lower frequency of ending up on the ventilator or dying at day 28. This was clinically significant, 12% versus close to 20%, so statistically significant as well. Of note, however, this didn't quite translate into a quicker hospital discharge, or quicker improvement to clinical status, but it did also show that there was a reasonably safe, a good safety profile in terms of there wasn't a difference in secondary bacterial or fungal infections in the tocilizumab arm.

The second study, which is of note, is the Remack study. Again, tocilizumab, sarilumab, versus usual care, essentially showing that there is an improvement in survival if you use these immunomodulators in addition to standard of care. This wasn't a superiority trial; they were using either toci or sari, and there's really no data showing one of them is superior to the other.

The next immunomodulator which we will review quickly is baricitinib. Again, this is - the evidence behind this has evolved over the last 2 years. The mechanism of action is that it prevents phosphorylation of key proteins and therefore leads to dampening the immune activation inflammation, again falling into the big category of an immunomodulator. It's FDA approved for hospitalized patients with COVID-19 requiring supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO, therefore, most of our critically ill patients will fit criteria for this. Not recommended if you already have underlying immunosuppression, such as a low lymphocyte count, low neutrophil count, or if you have underlying kidney disease. And again, contraindications are of course, if you have active TB, which could go completely wild if you use such a potent immunomodulator as baricitinib is. The data behind that? Remember, ACCT-1 was for remdesivir, ACCT-2 is far baricitinib, essentially comparing baricitinib plus remdesivir, versus remdesivir in severe COVID-19. Of note, steroids were not used in either of these arms, so just keep in mind that this wasn't steroids plus baricitinib, not double immunomodulators, just a single one. And as you can see here, there is a trend towards improvement in mortality, there is an improved - chance of improvement in clinical status at day 15 when you use the combination of bari plus remdesivir, compared to placebo plus remdesivir alone.

So essentially, the point being, you know, when you have critical illness from COVID-19, you should be thinking hard, not just about supportive management, but also about these new immunomodulators that have come to play over the last few months.

Back to you, Cam, for the final summaries.

Ms. Smith:
Alright, so our main take-home points. What do we know? We know that vaccinations work. We see patients coming into the hospital now who may have COVID-19, but no symptoms because they have been vaccinated. So it's very, very important to get vaccinated, to get boosted, it's going to significantly decrease your chance for severe and critical illness.

Dr. Mukherjee:
Completely agree, Cam. And you know, and the old proverb of, you know, prevention is better than cure, keeping patients safe. And, you know, we know that the vaccines, there's tons of data showing that it prevents badness from COVID-19. It might not be great in preventing the infection, but it definitely does a great job in preventing severe and obviously fatal disease. So vaccines, 100% as the first line of defense, along with, you know, non-pharmaceutical interventions, such as thinking about masking back again, given the surges and the variants that are continuing to wreak havoc in certain parts of the country, being a bit more sensitive about mass gatherings. I know all of us are very tired of being in this pandemic, but the truth is that there is still an ongoing surge, and this time, it's with influenza, with other respiratory viruses such as RSV. So the more we can prevent patients and educate the community from being sick enough to come into the hospital, the better care we can provide to the ones who, you know, might not have the defense with a vaccine, they're immunocompromised with stem cell transplants, which might not - the patients who might not do well, even despite having been compliant with their vaccines. So again, just want to emphasize vaccines, first and foremost.

Just continuing along the trend, the rest of the management, once you have a patient in the ICU, is triphasic, right, you have supportive care, the beautiful vent management, fluid management that Cam described, that coupled with antivirals, remdesivir, and others in that spectrum, and then, of course, the immunomodulators that we talked about. So it's a kind of a triphasic approach, supportive management, antivirals, immunomodulators, which have the evidence behind them to support care.

Cam, back to you, please.

Ms. Smith:
And I thank you so much, Vikram, for all of that, especially regarding the masks. You know, we want to protect others. You know, you may be extremely healthy, but not everybody around you is.

And the other thing I wanted to say is that we go into this field of medicine because we're lifetime learners. And, you know, part of lifetime learning is that you're keeping up with studies, you're keeping up with best treatment scenarios. And so there are still so many studies to be done on COVID. There's still so much more data to rifle through. And there's still so much to learn about long COVID and the eventual repercussions of, you know, what getting, you know, one strain versus another. So we're still going to always be learning about this. It's still very new.

Dr. Mukherjee:
Agree, Cam. And you know, I think it's very important that we keep up, it's still very new, to keep up with evolving evidence. There's still a mountain of evidence that continues to be published and presented, and it behooves all of us to be very aware and up to date and, you know, change our practice patterns in - with the backing of the evidence that ensues.

But in the meantime, you know, we want all of us, all of you, to be safe. And, you know, thank you for joining this session.

Ms. Smith:
This concludes our program. Thank you, Vikram, and thanks to our audience for participating today. Be sure to click on the continue button below the slides to earn your CE/CME credit.

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