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MULTIMEDIA

International Respiratory Infections Society COVID Research Conversations: Podcast 2 with Dr. Michael S. Niderman and Dr. Edward J. Schenck

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Edited Transcript

This conversation was recorded on January 6, 2021.

DR. RAMIREZ

(1) Well, thank you for joining us today for another session of COVID-19 Research Conversations, and today the conversation is going to be with two friends from New York City. I want to ask Mike and Ed to introduce themselves, and then we'll begin the presentation. Mike?

DR. NIEDERMAN

(2) Well, thank you, Julio. It's really a pleasure to be able to do this. My name is Mike Niederman; I'm a Pulmonary Critical Care specialist at Weill Cornell Medical College and New York Presbyterian Weill Cornell Medical Center in New York City. I'm the Clinical Director and Associate Chief in the Division of Pulmonary and Critical Care. And with me is one of our star intensive care colleagues, Ed Schenck; I'll let him introduce himself in a moment. I've been involved in a number of different activities throughout COVID, some administrative, some clinical, more outpatient than inpatient, some inpatient work in the ICU, some video work in the ICU, and again, all the outpatient issues that we're going to talk about as well. And I'm very much involved in discussing clinical trials and focusing more recently on the problems of the patients who've had COVID and are recovering. But I'd like to introduce Ed Schenck, who's been a key inpatient doctor, and particularly key in organizing our participation in a number of clinical trials. Ed?

DR. SCHENCK

(3) Thanks, Mike; thanks, Julio. I'm Ed Schenck; I'm an Assistant Professor of Clinical Medicine at Weill Cornell. I'm a full time practicing intensivist/clinical researcher, and I see the role of clinical research with COVID-19 as the intersection between clinical trials, data science and translational science. We tried at Cornell in the spring surge to answer the call for inpatient data about the pandemic, getting our intensive care unit and our pulmonary service up and running with as many clinical trials as possible, but also generating data at the same time. And that happened through a lot of the work at our institution and also internationally. So, there's a lot of interesting things to talk about. Thanks very much.

DR. RAMIREZ

(4) Excellent. Just jump directly into lessons learned, Mike.

DR. NIEDERMAN

(5) Great! Well, early on, as I'm sure you remember, New York City was at the epicenter of COVID-19. We saw very many patients—probably something of the order of 1,300 patients—in the springtime, and we have another surge going on now, but the numbers are not quite as dramatic. Currently, we probably have something like a quarter as many patients in the hospital as we did in the Spring. Likewise, in the ICU, we have fewer than in the Springtime, and interestingly, fewer patients are mechanically ventilated in this current surge. Early on, I worked with one of our other faculty members, Meredith, to summarize our experience treating COVID. We took the possibly provocative stance that what we learned about how to manage patients in our specialty of pulmonary critical care during this time will have long-lasting and, I would argue, permanent changes on the practice of our specialty. Once COVID is long gone, many of the things we've learned will serve us well going forward, and there will be important changes in how we practice.

(6) In this article, we summarize the changes in outpatient care, inpatient care, and medical education.[1] I don't want to go through everything exhaustively here, but I want to touch on a couple of things. In outpatient practice, we have of course, as I'm sure all of you have, had to rely extensively on telemedicine; I think that will continue going forward. I think we were reluctant to do telemedicine in ways that we're currently doing it. We've become much more comfortable, we're doing a lot more, and we're following patients closer than we thought we could with telemedicine. And I think that for some patients, it gives them access to care that they didn't have before. One of the things that we were worrying about then and still worry about is that patients are so scared to come out and go to the office, or so frightened by the technology of telemedicine that they don't contact the doctor. And we're worried that some of our patients with serious respiratory problems might neglect those problems and not manage them completely effectively because of the concerns that are generated by COVID. There are multiple long-term sequelae, which I think are going to dominate our outpatient practice of pulmonary medicine—again, long after COVID is gone. We've seen patients with unexplained dyspnea that we can't really account for physiologically; cough has been a very prominent symptom that's persisted in some patients for months and months, and although some of that may represent bronchospasm, we don't understand all the factors that contribute to cough; we've seen persistent lung infiltrates that can lead to fibrosis, organizing pneumonia, and persistent need for oxygen even in the absence of some of the lung infiltrates. And we've established a post–COVID-ICU multidisciplinary care program. We had

a fledgling post-ICU clinic before COVID, but that's been ramped up dramatically because of all the survivors that we've had from the ICU and all their ongoing needs. And this clearly has to be a multidisciplinary effort.

(7) These are some of the things that we've had to deal with, but again, I think we will continue to deal with them. The problems after COVID are well documented in many studies. In this particular study, for example, nearly 90% of patients who were hospitalized in Italy had at least one persistent symptom two months or longer after initial onset.[2] We also know that the severity of the COVID doesn't necessarily correlate with the persistence of symptoms. Patients who have symptoms persisting may have had mild COVID, and people with more severe COVID may be debilitated but may not have some of the same persistent symptoms. In addition to respiratory symptoms, they can have fatigue, chest pain, cardiac arrhythmias, and we're learning about the multi-system nature of the sequelae of COVID. In our hospital, one of our pathologists has done a very interesting multi-center autopsy study; they demonstrated that 84% of patients at autopsy had a tracheobronchitis, and there were virus elements in the airway epithelium and type II pneumocytes.[3] In this picture from the autopsy (**Figure 1**), you can see an ulcerated lesion in the trachea. Our clinical impression from people who've survived COVID is that many of them have persistent airway symptoms. We see that in the office after they've left the hospital; they have persistent coughing, and some respond to bronchodilators, and sometimes corticosteroids treatment as if it's bronchospasm. But nowadays, it's much more refractory. And I think we're going to learn more about the mechanisms of cough in general, but particularly the cough related to COVID.

(8) On the inpatient side, at the peak of the pandemic in the Spring, we had about 250 patients in ICU. Our hospital is built with an ICU capacity of about 110–120. So, to accommodate those numbers in the ICUs, we had to redefine what an ICU is; we took the elements of the ICU and put them in places that were not traditional ICU settings. We worked very hard to establish multidisciplinary teams with different care responsibilities. For example, anesthesiologists were not doing elective surgery at the time, so they were available to help us as part of an intubation team. Physical therapists were helping us proning patients who needed prone ventilation as treatment for ARDS. And we had other people from different disciplines—neurology, critical care, cardiac critical care, and surgical critical care—working, again, to be part of a multidisciplinary ICU team. We also had some of the surgical interventionalists help us as a line placement team. But we also didn't have an exclusively medical or exclusively surgical ICU team taking care of these patients; we mixed a number of disciplines, and we included hospitalists as well.

(9) There are new approaches to treatment of ARDS that I'm going to let Ed talk about. We used, of course, non-invasive ventilation and high-flow nasal cannula. I think we've become more comfortable with using that as a way of treating patients and delaying intubation; early on, we were more reluctant to do that than we are now. We've certainly focused on multi-system organ failure. And I think that all of this has reinforced to us the importance of viral causes of community-acquired pneumonia. I'll refer you to this article, which some of our colleagues wrote in the *American Journal of Respiratory and Critical Care Medicine*, talking about ways that we developed to deal with ICU needs in a non-traditional fashion.[4] I think that fast-file response will probably continue as we go forward. I'm going to let Ed talk a little bit more about ventilation, but this is a phenomenal paper that he was part of.[5] And the far right column here (**Table 1**) looks at the respiratory mechanics and respiratory support in 270 patients with respiratory failure and COVID that were treated in our hospital. And I think I'll just lay the groundwork for some of the therapies, but I like this paradigm of breaking COVID down into different phases. When we look at treatments that we consider good in the early stage versus the late stage, in mild disease versus severe disease, I think we also have to look at those phases as relating to the events that are happening—meaning that early on, in milder disease, there's a predominance of viral illness that's making the patient sick, and as that viral illness begins to fade away and is replaced by an inflammatory response, that's the factor that's making patients sick. So it stands to reason from that pathogenesis that antiviral therapies, which include, for example, monoclonal antibodies and convalescent serum antibodies, are going to be most effective early in the disease with milder illness when the virus is predominating. And in later phases of the disease, when the patients are sicker, and when they have inflammation predominating, an anti-inflammatory therapy makes the most sense.

(10) We again reinforced all the basic principles of critical care in the treatment of ARDS: mechanical ventilation, non-invasive ventilation, high flow and, of course, the importance of negative pressure ventilation, and some of the prophylaxis that we need to do and thinking about complications like ventilator-associated pneumonia, venous thromboembolism, catheter-related bloodstream infections, stress, GI bleeding, and other issues. So now, I'm going to turn the podium, if you will, back to Ed, and I'll let him talk about what he's learned, particularly about the inpatient and ICU management of these patients, because he's been involved in some phenomenal studies that have helped elucidate principles in critical care that we now understand better, and I think will form the basis, as I mentioned earlier, of changing our practice going

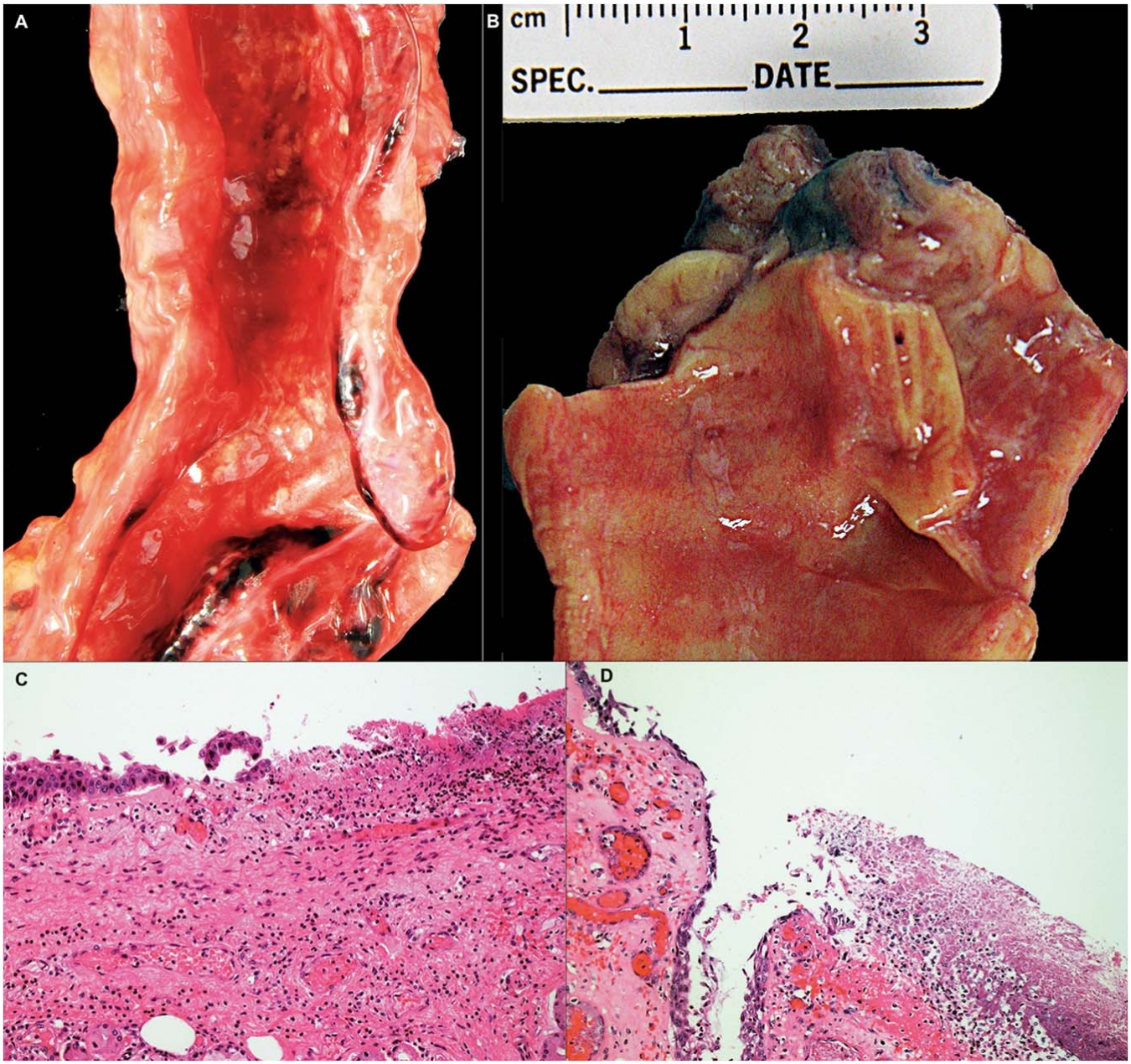

Figure 1. Tracheobronchial inflammation in COVID-19: **a**, **b** are gross photographs of trachea and main stem bronchus showing circumscribed white patches of 2.0–3.0 mm in diameter. **c** Microscopy of these lesions show ulceration with acute and chronic inflammation, **d** some with associated necrosis and fibrin. (**a**, **b** Gross photograph, Hematoxylin and eosin stain, **c** x50 and **d** x100.)

Table 1. Respiratory mechanics and respiratory support in 267 patients with respiratory failure and COVID-19 treated in a New York hospital.[5]

	New York City, NY, USA
Respiratory Support*	
Invasive mechanical ventilation	267 (100%)
Non-invasive ventilation	51 (19%)
High-flow nasal cannula	0
PaO_2/FiO_2 ratio	103 (82–134)
Compliance, mL/cm H_2O	28 (23–38)
Plateau pressure, cm H_2O	25 (21–29)
Positive end-expiratory pressure, cm H_2O	10 (8–12)
Tidal volume, mL/kg PBW	7.0 (6.1–8.1)
Prone positioning	108 (40%)

PaO_2=partial pressure of arterial oxygen; FiO_2=fraction of inspired oxygen; PBW=predicted bodyweight.
*Some patients received more than one type of respiratory support.

forward.

DR. SCHENCK

(11) Thanks very much, Mike. I'm going to present some of our observational data that we have been putting together and some of what I think about regarding the natural history of critical illness in general and with a focus on COVID. At Cornell, in the immediate first surge, the first priority for all of us as practicing intensivists was scrambling to take care of this massive surge of patients with respiratory failure, and making sure that the basics were done well. That means getting people appropriate oxygen therapy, intubation, and appropriate support when on the ventilator, and then dealing with other organ failure supports as they emerged, such as renal failure or cardiovascular failure. And as that was happening, and as we extended our capacity beyond our usual ICUs, it was really an administrative *tour de force* from the top of our institution through our practicing doctors coordinating expansion of ICU care beyond our regular ICU walls. There were redundancies in terms of who was caring for patients, and also which patients would be best served in which environment. We had a kind of hub-and-spoke mentality in terms of where patients were initially resuscitated and then moved into other types of care locations after the initial resuscitation period.

(12) So there were tiers of critical illness in terms of how patients would be distributed, and some of that will never make it into an actual journal because it was kind of difficult to define, but it was potentially lifesaving for a lot of patients who were moved from operating rooms to main ICUs and out to pop-up ICUs, and it was really marvelous to see. So, clinical care was the top priority, but at the same time, we wanted to generate treatments and data and get involved in clinical trials, because the treatment of this disease had so many unknowns. I served on our medical college's steering committee, assigning priorities to our clinical trials because there was competition among pharmaceutical companies and from NIH and other organizations in terms of which trials would be entertained and which would add value. So, in a very deliberative process, we really prioritized our own internal investigator-initiated studies to highlight our own emerging talent, but also the large phase-three multicenter studies that had good scientific rationale, much as Mike outlined in terms of the antiviral phase, the anti-inflammatory phase of the virus, and also the clinical phases of the disease, from the outpatient to the moderate inpatient disease to the severe or critical inpatient disease, making sure that there were options for patients within each phase of the disease and within mechanistic classes, being antivirals, anti-thrombotic agents, and anti-inflammatory. Really, thinking proactively as an institution about filling up each one of those buckets was really important. This observational data is a combination of how we adapted our ICU research infrastructure to the expanded ICU capability, so we had to adapt how we collected and analyzed our data.We also participated in several multicenter observational studies at the same time, providing data to larger groups. So I'm going to get into my talk now. So this is understanding the natural history of severe COVID.

(13) The challenge with severe COVID-19, or any sort of disease that requires organ failure support, is that the disease process takes the form of an arc, and the job of an intensivist to get patients through these sorts of disease is to support failing organs as the natural history unfolds. And then, you also have anti-pathogen therapy and anti-inflammatory responses that can make the period of organ failure less severe—or make the damage related to our organ failure–supportive therapies less severe—so less ventilator-associated lung injury, less delirium associated with sedatives, etc.—to get the patients through to the other side of the natural history. So, what we tried to do here at Cornell was to understand the natural history of COVID-19 ARDS a little

better. The challenge of understanding the natural history of severe critical illnesses is that patients don't necessarily all arrive at the ICU at the same point in their clinical course, although it seems as though with severe COVID, they usually arrive in a hyper-inflammatory state, although not the traditional cytokine release syndrome that was defined earlier. In a stereotypical chest X-ray of a COVID-19 patient with ARDS, with mechanical ventilation treatment, you see diffuse bilateral patchy opacities in all lung fields. However, very early on, doctors saw that not every patient actually fit this bill in that not everyone had diffuse bilateral patchy opacities, despite marked degrees of hypoxemia, so we really wanted to understand the variability. This is part of the understanding of the respiratory mechanics and gas exchange.

(14) This paper that we published in the annals of the American Thoracic Society was a research letter summarizing our early experience with about 260 patients requiring mechanical ventilation with severe COVID during our "surge" experience.[6] We broke this down by eventual mortality—we had an inpatient mortality of about 30% of our mechanically ventilated patients—versus eventual discharge, examining how a patient's mechanics on day 1 associated with the eventual outcome. And you can see (**Table 2**) that the P-values on the right are all greater than 0.05, so there were no statistically significant difference between any of the mechanical ventilation parameters that would predict eventual outcomes; this includes the amount of applied PEEP, the minute ventilation, the PEEP pressures; the plateau pressures were a little higher for patients who were eventually deceased, the PF ratios were little lower, and the compliance was a little lower, but none of this was statistically significant.

(15) What we did see, though, is that plateau pressures and minute volume exhaled slowly changed over time, and patients who were eventually discharged have a slight decrease in their trajectory, which the patients who were eventually deceased never had. So, that got us thinking about whether or not the trajectory of disease mattered more than upfront inflammatory burden or upfront severity of disease. And the world now understands this, but early on in the pandemic, it was shocking to understand how much non-pulmonary organ failure there was with severe COVID-19. So these are some of the collaborative efforts within Cornell. We saw with our neurology colleagues that stroke was very common, not only in the critically ill population, but with our moderate patients as well. Myocardial infarction was very common, ARDS is extremely common, thromboembolic events, as highlighted by our hospitalist colleagues, were incredibly common with COVID-19, and renal failure, additionally, was very common.

(16) This is a paper from the STOP-COVID collaboration, to which we contributed about 90 of our early patients (there are about 8 publications so far from this group based out of Brigham and Women's.[7] The idea here is that organ dysfunction beyond respiratory failure was one of the key associations with poor outcomes. You can see[1] that these are individual organ failures—heart failure, liver injury, kidney injury, shock—and that all of these by themselves are associated with different risks of mortality, but you can also see that cumulative organ failure really has stepwise association with risk. And so, with this cumulative organ failure driving outcomes, it's a kind of tautology, because the more organs that are shut down, the worse you're going to do. But we decided to look at this in a different way using the SOFA scoring system to see whether there were any sort of novel subphenotyping mechanisms we could look at within our mechanically ventilated population.

(17) This is a Sankey diagram,[2] which is a little hard to understand, but these are good SOFA scores at the top in the white bar, with the darker bars representing higher severity of illness. This is from a Blue Journal paper from 2019 that looked at Andromeda Shock—cap refill versus lactate clearance in terms of resuscitation for sepsis—but the idea here is that over time, patients move through different levels of organ dysfunction.[8] An idea that I've been thinking about for a while is that a patient beginning at a middling level of organ dysfunction could improve, stay the same, or worsen (and the black bars represent death), so there are many different options for what happens as you move from state to state, and this can be repeated at every state. So what arc is the natural history of this type of organ dysfunction, and how many patients actually fit within these progression pathways?

(18) So we did this with our COVID-19 population in collaboration with our machine learning colleagues and informatics group.[9] We looked at our COVID population at the time of intubation, both at our primary institution at Weill Cornell and then repeated at Lower Manhattan, and then bucketed this group in terms of mild, intermediate, and severe baseline levels of organ dysfunction. We then looked at trajectory similarity through a technique called dynamic time warping, and then used hierarchical clustering after that in order to see whether the trajectories grouped together. So that means whether patients with differing levels of baseline severity of illness move together through that severity of illness in a similar fashion. What we found is that the organ dysfunction was additive—mild

[1]See Gupta et al.[7] supplemental content **eFigure 5.** Acute Organ Injury (https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2768602).

[2]See Zampieri et al.[8] **Figure 2.** Alluvial plot for SOFA category across time (https://www.atsjournals.org/doi/full/10.1164/rccm.201905-0968OC).

Table 2. Ventilator Parameters by Status, Day 1.[6]

Characteristic	Deceased, N = 90	Discharged, N = 170	p-value	q-value
PCO_2 Arterial	46 (38, 52)	44 (38, 52)	0.5	0.8
PO_2 Arterial	92 (75, 121)	93 (74, 130)	>0.9	>0.9
Minute Volume Exhaled	9.80 (8.33, 11.80)	9.30 (8.15, 11.35)	0.4	0.7
PEEP	10.0 (9.0, 12.0)	10.0 (8.5, 12.0)	0.3	0.6
Tidal Volume	450 (400, 500)	450 (400, 500)	0.8	>0.9
Peak Inspiratory Pressure	31.0 (25.0, 35.0)	30.0 (26.0, 34.8)	0.6	0.8
Plateau Pressure	26.0 (22.0, 30.0)	24.5 (21.0, 28.0)	0.2	0.6
PF Ratio	105 (84, 137)	117 (86, 160)	0.086	0.5
Tidal Volume / PBW	6.92 (6.24, 7.70)	7.06 (6.36, 8.31)	0.2	0.6
Static Compliance	28 (23, 36)	29 (22, 40)	0.4	0.7
Driving Pressure	15.0 (12.0, 18.2)	14.0 (11.0, 16.5)	0.065	0.5
Ventilatory Ratio	1.93 (1.51, 2.32)	1.80 (1.47, 2.30)	0.6	0.8

severity of illness was respiratory failure and neurologic dysfunction; intermediate severity of illness was additive cardiovascular dysfunction; and most severe was additive renal failure. We did not see almost any upfront liver failure or upfront coagulopathy in the severe COVID patients, and we did not see kidney failure without cardiovascular failure.

(19) There were only 2 defined trajectories within each organ dysfunction baseline category, a very simple "worsening" or "improving." So the red line (**Figure 2**) is the worsening group—over time, the patients themselves had a SOFA trajectory that was increasing. The blue line is the improving group, whose SOFA values were decreasing. And this repeated within each bucket of mild, intermediate, and severe. And we saw that if the SOFA scores of the mild group were worsening (red line, **Figure 3**), their outcomes were actually worse than those of patients with multi-system organ failure at baseline, so the trajectory of organ dysfunction mattered much more than the baseline severity of disease because the blue group, even with multi-system organ dysfunction, had improved outcomes.

(20) And so, just to summarize, we found that non-pulmonary organ dysfunction is important for COVID-19, and that additive non-improving organ failure drives outcomes. This has us thinking—now that we're in the era of standard dexamethasone treatment, which we were not in the Springtime—in the face of additive or non-improving organ dysfunction, what are the next steps for immunomodulation? Because it seems that this is not an ongoing viral-driven process, but dysregulated immune response. Some patients are refractory to corticosteroid therapy, meaning that they have progressive organ dysfunction that is not fully addressed by corticosteroid therapy; some of these additive or new organ dysfunctions, unfortunately, are ICU-acquired problems like secondary infections and thromboembolic disease events. So it's not just a dysregulated immune response, but this is kind of where the next stage is, as far as I can tell.

DR. NIEDERMAN

(21) Right, and Ed has also done some really interesting work on mechanical ventilation. One of the controversies has been whether the ARDS of COVID is the same or different from traditional ARDS. Some people have observed that the lung compliance in some of the COVID patients was not as low as in traditional ARDS. In Ed's study of the ICU patients, lung compliance really was pretty much the same as ARDS, but some people speculated that patients who had respiratory failure with more normal lung compliance were primarily sick because of pulmonary vascular disease. We know that these patients did have microthrombi. There was, of course, a lot of interest in anti-inflammatory therapy, in addition to dexamethasone using anti-IL-1, treatments like anakinra, IL-6, tocilizumab, using JAK inhibitors like baricitinib, and all this has been really interesting. There's been a number of novel therapies that we have not been involved with; for example, there was a study primarily conducted in Florida looking at Ivermectin because of its potential antiviral and viral binding effects and mediator effects. So there's a lot of therapies, but I think we stuck to pretty traditional therapy, and as Ed mentioned, corticosteroids have really established a key role for inpatients who need oxygen. As you know, in the recovery trial, the benefit of steroids was not present for those who did not need oxygen. We use a lot of remdesivir, and there's been interest in other clinical trials of anti-inflammatory therapy, but nothing has been established in the mainstream for all patients right now. Ed, do you want to say anything else about our clinical trials?

DR. SCHENCK

(22) Yeah, so our current clinical trial framework is in

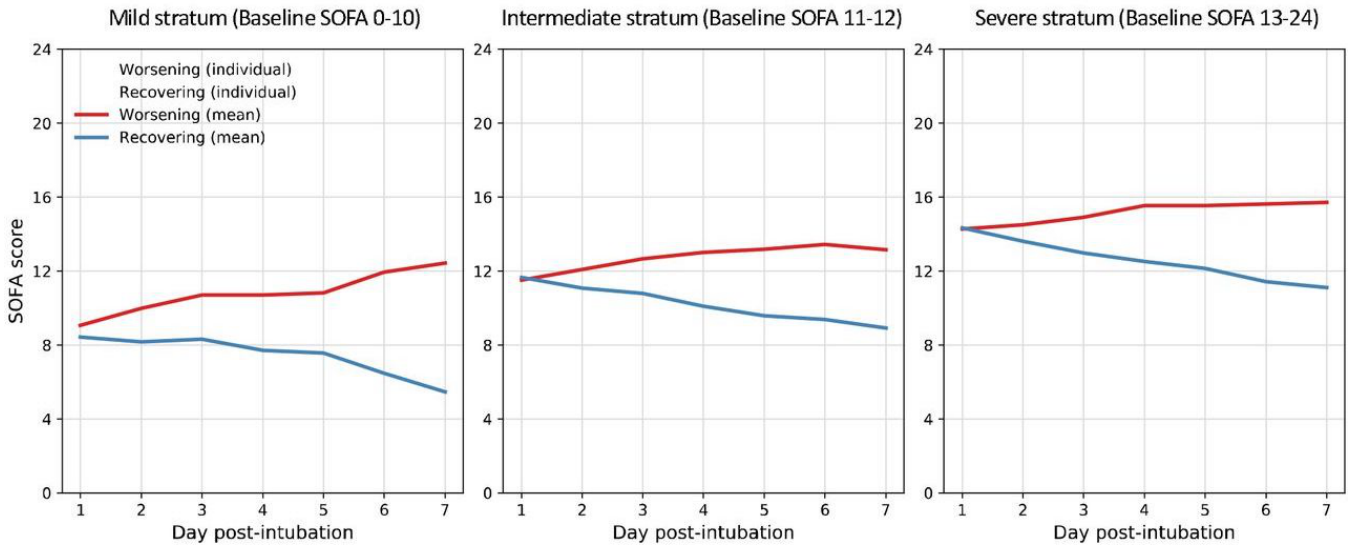

Figure 2. Distinct worsening and recovering subphenotypes.[9]

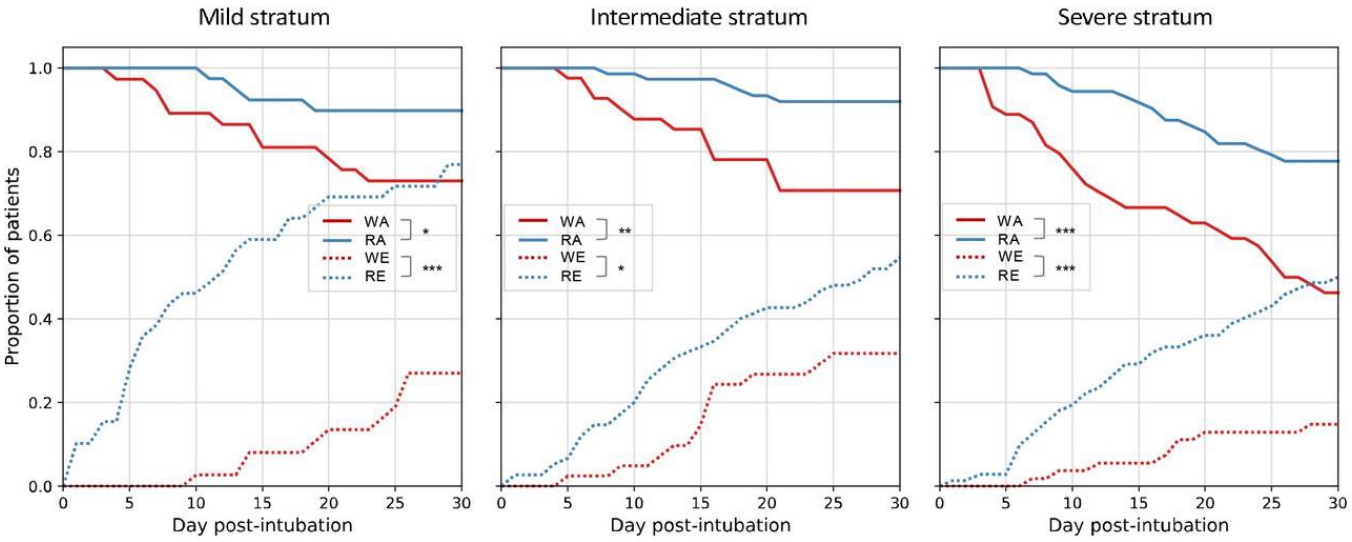

Figure 3. Trajectory predicts outcomes. WA=worsening subphenotype alive; RA=recovering subphenotype alive; WE=worsening subphenotype extubated; RE=recovering subphenotype extubated.[9]

the background of dexamethasone and remdisivir as the standard of care. With our moderate and severe patients, we are participating in the NIH's ACTIV-1 platform trial, which is studying a combined bucket of anti-inflammmatories, from infliximab to CCR5 inhibitors and CTLA-4 inhibitor (I think is the third one). And in addition to that, we have a convalescent plasma trial called CONCOR-1, which is wrapping up in the near future, an anti-thrombotic trial that is investigator-initiated, and a phase one cellular therapy trial in an early phase that's investigator-initiated. We're also opening up an anakinra study for the pre–mechanical ventilation piece. We're trying now to hit the different immunomodulatory pathways, thrombotic pathways, and other pathways as patients progress.

DR. NIEDERMAN

(23) Yeah, but I think it's really important to emphasize that all of these preliminary data and mechanisms are still trials, and they're not the standard of care for everybody. And I think that in your own institution, it's really important that you participate in organized data collection and clinical trials, rather than, say, you read a paper that looked good; now you're going to change the way you practice for everybody—I don't think that's really the way we ought to be doing things. So we certainly have learned a lot, and I think the rapidity with which these trials got done in the ICU is another very important lesson that we've learned during COVID that we hope will carry over moving forward. Particularly, also, the multidisciplinary nature of these studies—cooperation between cardiology, critical care, neurology, particularly infectious diseases, even rheumatology and hematology—has been very impressive during this time, and I think it's, again, established a new paradigm that we can use going forward.

(24) I just want to finish up the review of how COVID has changed things by talking a little bit about what impact it's had on our medical education experiences, and I don't think we're unique in this. Like this conference, almost all our conferences are now being done by internet. A lot of us who used to drive ourselves crazy, running through airports and traveling all over the world are asking ourselves, "gee, do we really need to keep doing that?" I mean, it may be interesting; it may be fun, but it's certainly not as necessary as we thought. We've had some very effective educational experiences via the internet, in our training programs, both in internal medicine and in pulmonary critical care. Prospective trainees have been interviewed by Zoom; they're not making site visits anymore. One of the things that I've wondered about, and I don't think there's a good answer, is when people watch what we do, has that increased or decreased the appeal of critical care as a specialty? I think on the one hand, it looks really exciting, and it's really nice to be at the cutting edge of medicine. On the other hand, looking at some of my colleagues, and the exhaustion and the emotional stress of working with these patients, and the incredible hours they've had to work—that may not be an appealing model to all trainees.

(25) I think that one of the lessons we've all been aware of is that we need to focus on the work-life balance, family life, and the emotional stress of working in the ICU. This has been an ongoing crisis in the hospital, and in particular for critical care doctors. And I think that, although we were aware of this always, COVID has made us even more aware of the importance of having some sort of plan for emotional stress relief and trying to deal with wellness in the physicians and the care team who take care of COVID. So, I would just conclude the formal part of this presentation by saying that we've learned a lot during COVID; I think it's changed the way we practice, but I think a lot of this will carry over going forward. And I think for us, it's been an exhausting time, but it's also been a very exciting time, particularly when you have someone like Ed summarize all the activities we've been involved with and all the progress that's been made in what has really been a remarkably short time—less than a year. So I think this has been one of the most exhausting and yet exhilarating times in our specialty, and I hope that some of that's come across and we were able to share some of those ideas with you today. Julio?

DR. RAMIREZ

(26) Excellent—I think that's a lot of lessons learned that you just compacted into 30 minutes. And now, the second part of this conversation is how do we see COVID-19 in 2021. For instance, what's going to happen with therapy; when are we going to get new therapies? You already mentioned the post-COVID clinic they're developing in almost every place—how are we going to deal with these patients and what do we think is going to happen there? There are all these COVID barriers emerging in all these places around the world; what's going to happen with monoclonal antibody plasma, and of course, the critical issue, what's going to happen with vaccines? Of course, there is no clear data, but I would like to throw some of these concepts to both of you and ask how you see some of these areas for 2021?

DR. NIEDERMAN

(27) Well, I hope the biggest thing that's going to happen in 2021 is we're going to be seeing COVID in the rearview mirror. I'm really hoping that with vaccination, we're going to be finally turning a corner here, seeing less and less of this. That hasn't really happened yet, and I think we're all worried that for some of the reasons you said, maybe it will, and maybe it won't, but I think certainly it's something that we've all been looking forward to. What I anticipate is a lot of refinements

in what we do because I think the studies that are being done now, compared to the studies that were done a year ago, are much better controlled; the populations are better defined, and the timing of the intervention is more specific. There's a number of examples of clinical data that are positive now for therapy that weren't positive in the past: convalescent antibodies are a good example; early studies on tocilizumab were negative—some new ones are positive. So I think we're probably going to learn a little better when to apply these therapies in which specific populations, whereas I think earlier studies were broad strokes just trying to see if anything worked. I think that that was an effective strategy because it certainly cemented for us the value of corticosteroids, which were controversial as a treatment for viral infection prior to COVID. So I see it as a focusing down; I'm not sure what other therapies will emerge, but as Ed said, in our hospital, we're still sticking to the basics while we add on other therapies to see whether we can improve outcomes and define subsets that need those therapies. Ed, what are your thoughts?

DR. SCHENCK

(28) So, in terms of the rearview mirror for COVID, that's what I'm hoping for. If you look at the natural history of respiratory viruses' relationship with humanity—flu being an outlier, but using other coronaviruses as a model—antigenic drift does not really lead to sustained severity of illness. There's a beautiful paper in *Science*, published last week, that's a modeling study comparing the natural exposure history of other kinds of coronaviruses in the course of a population. Basically, about 90% of the population is infected by the time they're 4 or 5 years old, and reinfections are common but associated with minimal symptoms. So, even with the setting of antigenic drift, in terms of what's happening with the spike protein with all of these variants, viruses are not out there to kill us; they're out there to reproduce—the goal of a virus is just to continue its own genome. So, the selective pressures for the relationship with our immune system are probably such that it will evolve to a point where it can bounce from host to host happily over the course of a lifetime, producing symptoms that enable it to bounce—meaning cough and cold-like symptoms through which to propagate itself—but potentially our immune system, in terms of limiting collateral damage and organ dysfunction, will reach a steady state. So I think that if you look at other coronaviruses as an example, or if you look at other respiratory viruses, the most likely long-term outcome is that this will become endemic and that we will be looking at the severe COVID respiratory failure, as Mike said, in the rearview mirror.

(29) However, in terms of what lessons we learned about trials and how to adapt therapies quickly and expand critical care to large, unanticipated populations, I think those are going to be so important because there will potentially be another coronavirus or a different strain of the flu or an as yet unknown respiratory virus. Using adaptive platform trials as a new standard to test multiple therapies in large populations and what the NIH is doing with the ACTIV platform trials—hopefully, this will not be in our rearview mirror anytime soon. Hopefully, this will be the standard, and we'll be able to define diseases better; we'll stop calling things traditional ARDS—we'll call it viral ARDS or coronavirus ARDS or flu ARDS or staph pneumonia. And we'll have adaptive platform trials for those specific sources of respiratory failure, as opposed to these nonspecific syndromes, learning as we go along for specific diseases. That's what I hope the research community takes away as a real positive from this pandemic experience.

DR. NIEDERMAN

(30) I think that's a great perspective. I do want to say one more thing about vaccines. I think we're all pretty hopeful about the vaccines and what they're going to do for this disease, but I think we've got to be a little bit circumspect until we learn a little more. I'm beginning to read articles that say, "as soon as you're two weeks post your second vaccination, throw away your mask, go hug your kids, go visit your friends, and start going out to dinner." We don't know that yet. And I think we've got to be really careful before we overestimate the potential of the vaccines and be sure that we're not spreading the disease or creating other problems. I think we've got to get there slowly. Today is two weeks after my second dose, but I haven't thrown away my mask yet, and I think I'm probably going to be very cautious until I begin to see the frequency of the disease decline, hospital beds being open, and hospital and ICU capacity being closer to normal because in the rare event that the vaccine doesn't protect you, you want to be treated in an environment that's prepared to take care of you.

DR. RAMIREZ

(31) You mentioned, Ed, that you started to prioritize—you made a ranking of the clinical trials—and I think that happened with COVID-19 in almost all universities. Until now, everybody had their own area to treat and you were selected as an investigator based on your area, but with COVID-19, as you said, all the companies—even the NIH—were looking at multiple investigators, and at a lot of universities, the ID physicians, pulmonary physicians, critical care physicians, anesthesiologists, and even rheumatologists were all doing critical tasks. How did you develop the system to make sense of these 75 studies with everybody looking at the same type of patient?

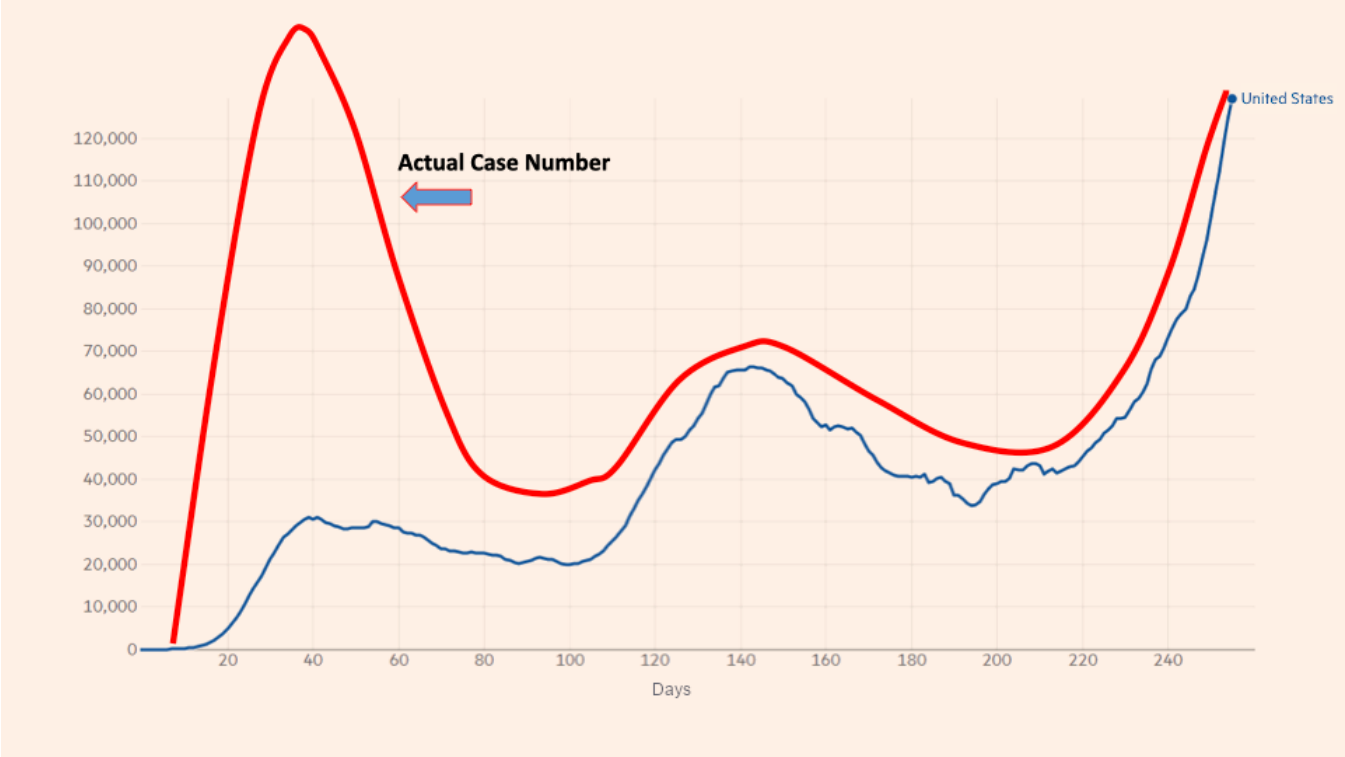

Figure 4. Recorded vs. real COVID-19 case numbers in the United States. Recorded data (blue) from *Financial Times* (https://ig.ft.com/coronavirus-chart/); modeled actual cases (red) from Dr. Schenck's as yet unpublished research, kindly provided by the author.

DR. SCHENCK

(32) So we had this steering committee set up with members from various disciplines—ID was a strong presence; I was a representative for pulmonary critical care; we also had representatives from rheumatology, general internal medicine, hematology, and oncology because of their prior clinical trials experience and because some of the molecules were actually from their area. As new protocols would come in, a member of the task force was charged with reviewing that protocol, evaluating it, and then presenting it to the rest of the group, with the overarching guidance that the 2 things we wanted to stress primarily were large, well-funded phase III studies with a mechanism that our group was enthusiastic about, and then also bearing mind what was already approved. So, if it was approved once already, it would preclude other competing studies within the same timing, framework, or mechanism. Sometimes the timing mattered, and we also wanted to make sure that our studies included different phases of the disease treatment: the outpatient phase, early moderate inpatient phase, and the severe phase. The other responsibility of the steering committee was to weight our own investigators; if they had a good idea, something that could lead towards institutional advancement, then we would weight that similarly to a large phase III study.

DR. NIEDERMAN

(33) And they did a great job; the principle that was followed was not only providing for patient needs, but really good science. They resisted the temptation to to make the studies servants of individual investigators and made the choices for the greater good of the patients in the community.

DR. RAMIREZ

(34) Very good! And you both mentioned that during the second surge, there have been fewer patients in the hospital and fewer patients in the ICU. This is happening globally; why is it that there are more cases of COVID, but fewer patients in the ICU?

DR. NIEDERMAN

(35) I don't know the answer; I would like to believe that we've learned how to better manage these patients. I can tell you that my view has changed 180 degrees. I was involved in an NIH workshop probably 15 or 20 years ago about the original SARS epidemic, and what had come out was that 20% of all the people who got SARS were health care workers, primarily intensivists and respiratory therapists, because they were intubating patients late, they didn't have the opportunity

to use quite as much protective equipment, and they were often contaminated during the intubation process. One of the conclusions, then, was that if a patient has any borderline respiratory failure, you should intubate them early rather than wait and be in an emergent situation that would be a great risk to the staff. But we've completely changed that view, and we've certainly realized that some of the early gung-ho intubations were probably not necessary and may have actually contributed to some of the long-term ventilation. The more widespread use of corticosteroids and remdisivir probably had a positive impact. I would hesitate to say that the virus has become less virulent. But I think we're all grateful for the fact that the ICUs, although they're certainly stressed, aren't stressed to the extent that they were in the Spring. On the other hand, I'm just speaking from our experience here in New York; when you look at news reports, what's happening in southern California, for example, doesn't seem like what we're seeing here.

DR. SCHENCK

(36) I have another slide here that addresses this question to some extent (**Figure 4**). The testing dynamic has completely changed our perception of the case numbers, so this is a curve across the United States, and you can see a shallow hump in March and April, but in order to get tested in March and April, you had to be nearly critically ill, coming into the emergency department and destined to be admitted to the hospital. If you weren't sick enough to be admitted to the hospital, you didn't get a COVID test, so the actual case number was potentially miscounted by a factor of 10 to 20 in the hardest-hit cities in March and April. So the idea that the dynamic has changed so much could actually just be an artifact of testing, that we're picking up minimally-to-asymptomatic cases now that we weren't detecting at all in the early part of the surge. Additionally, for hospital-related outcomes, there's emerging evidence that inpatient mortality is completely dependent on the amount of community spread; there are some preprints circulating right now. The amount of hospital strain—meaning the choice to admit patients or not because of how many patients are already in the hospital—is actually a key determinant of what your inpatient mortality looks like. So, if you have the luxury of being able to admit patients who are less severe, your inpatient numbers and ICU numbers are going to look better. So, if you have a low community burden of disease, you're identifying cases in real time, and you have a hospital that's not burdened, you can admit a patient, give them a few days of oxygen, a few days of dexamethasone, and send them home, whereas if they were left at home, they probably would have done OK as well. But that makes it look like your inpatient numbers and treatment strategies have really made a difference.

DR. NIEDERMAN

(37) The only thing about that is, at least in our hospital, in spite of the liberalized use of the hospital in the diagnoses, we actually have a total number of inpatients much lower than we had in the Spring, so something has changed.

DR. SCHENCK

(38) Yeah, but I think it's related to the actual numbers within the community.

DR. NIEDERMAN

(39) Alright, Julio, thank you so much.

DR. RAMIREZ

(40) It was a pleasure; thank you, both of you. We'll keep in contact. I'm sure that the audience is going to enjoy your presentation and your insight into COVID last year and COVID this year.

DR. NIEDERMAN

(41) And of course, the other exciting thing about this is that we've had young investigators like Ed who've really come into their own in this crisis, so it's a very exciting time indeed.

DR. RAMIREZ

(42) Thank you, both of you.

DR. NIEDERMAN

(43) Thanks a lot.

DR. SCHENCK

(44) Take care.

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