Good afternoon. I'm Commander Ibad Khan and I'm representing the Clinician Outreach and Communication Activity, COCA with the emergency risk communication branch at the Centers for Disease Control and Prevention. I'd like to welcome you to today's COCA call, Clinical Management of Critically Ill Adults with Corona Virus Disease 2019, COVID-19.

For participants using the Zoom platform to access today's webinar, if you're unable to gain or maintain access or if you experience technical difficulties, please access the live stream of the webinar on COCA's Facebook page at www.facebook.com/CDCClinicianOutreachAndCommunicationActivity. Again, that address is www.facebook.com/CDCClinicianOutreachAndCommunicationActivity. The video recording of this COCA call will be available immediately following the live call on COCA's Facebook page.

The video recording will also be posted on COCA's webpage at emergency.cdc.gov/coca a few hours after the call ends. Again COCA's web address is emergency.cdc.gov/coca. Continuing Education is not provided for this COCA call.

After the presentations, there will be a Q&A session. You may submit questions at any time during the presentation to the Zoom webinar system by clicking the Q&A button at the bottom of your screen and then typing your question. If we are unable to ask the presenters your question, please visit CDC's COVID-19 website at www.cdc. gov/covid-19 for more information. You may also email your question to coca@cdc.gov. If you're a patient, please refer your questions to your healthcare provider.

For those who have media questions, please contact CDC Media Relations at 404-639-3286, or send an email to media@cdc.gov. For more Clinical Care information on COVID-19, you may contact CDC's COVID-19 clinical Call Center at 770-488-7100. The Center is available 24 hours a day. Again, that number is 770-488-7100.

We'd like to remind clinicians to please refer patients to state and local health departments for COVID-19 testing and test results. Clinicians should not refer patients to CDC to find out where or how to get tested for COVID-19 or how to get COVID-19 test results. Also, please continue to visit emergency. cdc. gov/coca as we intend to host COCA calls to keep you informed of the latest guidance and updates on COVID-19.

In addition to our web page, COCA call announcements for upcoming COCA calls will also be sent via email. So please be sure to subscribe to coca@cdc. gov to receive these notifications and share them with your clinical colleagues. I would now like to welcome our first presenter for today's COCA call, Captain Tim Uyeki. Captain Uyeki is the chief medical officer for CDC's Influenza Division, and is currently serving as the clinical team lead for CDC's COVID-19 response.

In addition to presenting, Captain Uyeki will also introduce our guest speakers for today's call and moderate our Q&A session. Now, I'm going to turn it over to Captain Uyeki. Captain Uyeki, please proceed.

Thank you, Commander Khan. I'm very excited today to have two distinguished critical care physicians. We will have Dr. Michael Bundesmann. And he is the medical director of Respiratory Therapy Pulmonary and Critical Care Medicine at EvergreenHealth in Kirkland, Washington.

And this hospital was one of the most impacted early on in terms of cases of COVID-19 in the United States. We're also very excited to have Dr. Waleed Alhazzani, who is an associate professor in the

Department of Medicine at McMaster University in Hamilton, Ontario, Canada. And Dr. Alhazzani is the primary author of the Surviving Sepsis Campaign: rapid guidelines on the management of critically ill adults with Corona virus disease 2019.

And he will be giving a summary of those guidelines. So, I'll just start by giving a brief overview of COVID-19 for clinicians. Next slide. So, just to give some background in some large studies, the median incubation period from the time of infection to illness onset is approximately four to five days, but a wide range. So we continue to use this range of 2 to 14 days.

Over. Next. The spectrum of infection with SARS-CoV-2 virus is quite wide ranging from asymptomatic infection to symptomatic illness. And that can be mild illness, uncomplicated upper respiratory tract signs and symptoms to moderate, mild to moderate pneumonia without the need for supplemental oxygen to more moderate to severe pneumonia requiring supplemental oxygen and potentially other forms of oxygen delivery support. And then certainly critical illness and you'll hear about that by our presenters, which include respiratory failure, or ARDS, septic shock, multi-organ dysfunction and failure.

Next. So just as an overview, some-- one very large study of cases in China reported that the vast majority of patients with COVID-19 do in fact have mild to moderate illness, however, 19% had severe or critical illness. You know, of those 5% were critically ill requiring ICU admission. And then another large hospital case series from China, a 1,099 hospitalized COVID-19 patients, 5% overall were admitted to the intensive care unit. Next.

And this was the very first case series, small case series from Wuhan, China. 41 hospitalized patients with COVID-19. What this figure illustrates is the time from illness onset to hospital admission about a week, and then about one day longer to dyspnea, and a couple days later to the development of ARDS with a median time from onset to ICU admission of about 10. 5 days. Next.

So, what this slide illustrates is early data from cases of COVID-19 in the US showing distribution by age group, and also showing in the orange line their case fatality. And you can see that case fatality just increases a lot once you're about 55 and older and particularly 65 and older. Next. What this graph shows of same data is that there, by age group on the x-axis, you can see that hospitalizations occur in all age groups in adults, but that ICU, and so do ICU admissions. But ICU admissions and deaths are primarily concentrated in older adults.

And in particular, in those 60 years and older, 45% of the hospitalizations were in this age group, 53% of ICU admissions and 80% of deaths were in those 60 years and older. Next. Overall cases in China, case fatality was high in those with certain underlying chronic medical conditions and was highest among those with chronic cardiovascular disease but also high in those with diabetes, chronic respiratory disease, and cancer. Next. So, in terms of what are the signs and symptoms present at hospital admission, the majority of patients at hospital admission in different case series from China, Singapore, and some ICU case series in the US.

Most have fever, cough and dyspnea at hospital admission. But notably, in the two small ICU cohorts that have been published recently in JAMA and New England Journal of Medicine, about 50% had fever at admission. In other words, the absence of fever does not exclude COVID-19 at hospital admission or particularly at admission to the ICU. Next. What this slide illustrates is that sampling or the yield for detecting SARS-CoV-2 viral RNA is much higher in the lower respiratory tract.

The yield is higher in bronchoalveolar fluid. It's also-- it's next highest in sputum, and those are higher than in upper respiratory tract specimens. Next slide. So, laboratory findings at hospital admission most commonly is lymphopenia. Mild to moderate thrombocytopenia and leukopenia is present at a little more than a third of patients.

There can be elevation of C-reactive protein in a majority of patients, as well as elevation of hepatic transaminases in about a quarter or two, a third or more. This is higher in those who are more severely ill. Typically procalcitonin when it's measured at hospital admission is normal. In terms of microbiology testing, or viral or bacterial testing, there have been sporadic viral coinfections reported with SARS-CoV-2 infection, including influenza A and B viruses, parainfluenza virus. So the bottom line is that detection of a human respiratory virus does not exclude a diagnosis of SARS-CoV-2 infection or COVID-19 that coinfections can occur.

They don't appear to be very common, but they can occur. And that it does appear, at least in the data from China, as well as some of the early data from the US is that community acquired secondary bacterial infection is not common at all. And in fact, it's not reported in published case series. There might be case reports that you might hear now and then that have not been published. But typically, blood cultures are negative at hospital admission.

And this is different than what we have seen in the past with seasonal influenza or pandemic influenza in which secondary bacterial infection. Particularly secondary bacterial pneumonia is very common, or much more common with seasonal or pandemic influenza. So, currently, at least community acquired secondary bacterial infection appears to be uncommon with COVID-19. Next. So what are the laboratory abnormalities that are commonly seen in those who are more severely ill? Well, lymphopenia, I mentioned, also an increase in the neutrophil count.

I mentioned elevation of hepatic transaminases. We do see elevation of lactate dehydrogenase, procalcitonin, in more severe disease as well as CRP and ferritin can be elevated. When cytokines and chemokines are measured and they have been in some published case series, you can see increased serum levels of these pro-inflammatory cytokines and chemokines. And that in the published literature, there are higher plasma levels of pro-inflammatory cytokines such as TNF alpha, IL-1, IL-6 and chemokines such as IL-8, in those who are severe or critically ill compared to those who are not severely ill. And overall, there are signals that increase D-dimers and lymphopenia, severe lymphopenia, marked lymphopenia are associated with mortality.

Next. So this slide shows, illustrates, that increase in white blood cells, but particularly the neutrophil count are both significantly associated with fatal outcomes compared to survivors in one hospital case series from China. Next. This slide shows that relative lymphopenia appears to be more apparent in those with fatal outcomes versus those who are survivors. You do see lymphopenia in all these cases, particularly in the ICU, but the degree of lymphopenia may be more marked in those with fatal outcomes.

Over-- next. And this slide just illustrates again that D-dimers was a strong predictor of death when compared to other markers of COVID-19 severity. This is a Chinese case series. Next. So, I just wanted to summarize two recently published case series of critically ill adults in the US, one is a series of 21 that was published in JAMA recently, and one is a series of 24 recently published.

And both of these case series are from the Seattle, Washington area although they had slightly different populations. So the range of comorbidities was a little bit different in terms of one case series had a

much higher percentage of those with heart failure and COPD. This was particularly a source of these critically ill adults was mainly from a skilled nursing facility. And prevalence, the percentage of heart failure and COPD was much lower in the other case series, which derived patients really from the community setting. However, in both case series, the percentage of diabetes, kidney disease and interestingly enough obstructive sleep apnea, these were fairly high.

There was a slight difference in the time from illness onset to ICU admission is roughly about 4. 5 to 7 days. So not long, but there is a range. The mean age in one case series was 70 years and then the other was 63 years, but you can see there's quite a wide range of ages. So it's typically our primarily older adult, but there are middle aged and younger adults included.

And the typical complications that were observed were respiratory failure requiring mechanical ventilation in the vast majority of the patients, shock requiring vasopressors also in the majority of patients. And acute kidney failure was uncommon, but was present up to 19% in one of the case series. Cardiomyopathy, not in one case series, but 33% in the other. And I think Dr. Bundesmann will discuss this.

And then again, just pointing out that bacterial co-infection was very low. The one was likely to be hospital acquired, or at least that person had significant underlying co-morbidities, but basically not really observing community-acquired secondary bacterial infection. And overall mortality in both case series was quite high around 50%. Next. So just to briefly summarize inpatient clinical management, there is no proven FDA approved specific treatment for COVID-19.

Management is supportive care of complications. Next. And that corticosteroids should be avoided unless indicated for other reasons. There may be prolongation of viral replication. That's what we know from the MERS-CoV experience and seasonal and pandemic influenza.

There are a number of drugs under investigation in randomized controlled studies in the US. There are studies being announced every day or every week. And also in other countries and remdesivir is actively being studied. Also Hydroxychloroquine or Chloroquine, Lopinavir, ritonavir, there was a published study recently, but it's under investigation in a number of trials. And then host directed therapeutics such as IL-6 receptor blockers.

There are clinical trials underway and all these drugs have been used off label in an uncontrolled manner. But to date, we don't have any data that really prove safety or efficacy of any of these drugs. And so, more data are needed particularly from randomized controlled trials. Next. So with that, I just wanted to highlight that there are guidelines and guidance available.

The WHO has published interim guidance on clinical management of severe disease with COVID-19. And then Dr. Alhazzani will present a summary of the surviving sepsis campaign guidelines. I will also mention that forthcoming will be treatment guidelines led by the National Institutes of Health. And so, look for that in the next one to two weeks.

And with that, I'd like to turn it over to the next speaker, Dr. Bundesmann. And again, Dr. Bundesmann is the medical director of Respiratory Therapy, Pulmonary and Critical Care Medicine at EvergreenHealth in Kirkland, Washington. Over to you Dr.

Bundesmann.

Thank you so much for the opportunity to discuss our case experience at Evergreen. I really have to say that I can't be any more proud of our organization and how we have responded to the outbreak of COVID in our area. We've been dealing with our cases now since the first ones came into our hospital starting the end of February. And so, we have accumulated more than four weeks of experience now taking care of these patients in our ICU. And so, I'm going to share a couple of case examples that highlights some of the challenges that we have faced managing these patients.

Next slide. First, there's a disclaimer here that my slides and case examples, of course, reflect our observations in our hospital and my views and not those of the CDC. Next slide. The first case before I go into it, I should describe also our hospital for some context. Evergreen hospital is in a suburb, Kirkland of Seattle about 20 minutes outside of the city.

It is a approximate 320-bed hospital with a 20-bed ICU. Our ICU and the 20 beds for the most part is half critical care and then half used for step down, which is a mixed usage ICU that have mostly medical ICU patients being managed for sepsis ARDS, and a few surgical patients as well, as well some neurosurgical cases. And so in context of this, the first case that I'm presenting is a 47-year-old gentleman who presented quite early in our experience with COVID-19. This was a community acquired case of COVID-19. He was 47 years old and had seven days of URI symptoms and presented after having worsening shortness of breath for three days.

He was a generally very functional and healthy individual and had been working at another long term health care facility other than the one that received the most attention in the region and had underlying hypertension, obesity and untreated diabetes mellitus. He had no underlying history of cardiovascular disease, tobacco, or other pulmonary problems. His baseline medications included an ACE inhibitor, Hydrochlorothiazide and Carvedilol. Initially, when he presented to the hospital, he did not meet testing criteria for COVID-19 although it's highly suspected. And he was tested as soon as we were able to submit his samples for testing.

Next slide. Here are two chest x-rays of the patient at the time of presentation, and then four days later, which show a typical chest x-ray for many of our patients who had severe ARDS from COVID-19. These typically showed bilateral alveolar airspace opacities without pleural effusions, and often showed fairly rapid progression over the course of the first several days even after intubation and mechanical ventilation was instituted. Next slide. This particular patient, I think, serves as a good example of the prolonged hospital course and duration of illness and otherwise, fairly young patients who developed COVID-19 at his age of 47.

He was initially intubated and placed on lung protective ventilation 6 ml per kg, tidal volumes, and then required ventilation for days 2 through 14 of his hospitalization. Over those 14 days of mechanical ventilation, he required proning for nearly 13 of those days. He was able to be supported without the use of inhaled epoprostenol or Flolan, and it did not require neuromuscular blockade. His settings throughout most of this time, he typically had a PEEP of 10 to 14 FiO2 of 60 to 70, depending on the time that he was proned or supine. And he was ultimately extubated to high flow nasal cannula.

He's initially treated with antibiotics appropriate for community acquired pneumonia. He did not have initial procalcitonin checked although our practice has changed slightly, that the procalcitonin is negative and cultures are negative or discontinuing antibiotics after two days. He received a full seven days of antibiotics. He subsequently then received remdesivir under compassionate use before we had the clinical trial up and running in our hospital. And he received a 10-day course of remdesivir.

And he also received Hydroxychloroquine for a five-day course as well. He was ultimately extubated on his 14th day of the hospitalization, and by 21 days of hospitalization was roomed between the two room air. But he did have significant and profound neuromuscular weakness and even still requiring a walker now, four weeks out of the presentation, despite his good functional capacity and strength prior to hospitalization and avoidance of steroids, and neuromuscular blockade. Next slide. Some notable findings on his labs at the time of admission.

He did have a respiratory pathogen panel that was negative for other co-infections and nasal pharyngeal sample was obtained from this patient, and it resulted four days later detecting the COVID-19. He was one of our initial patients admitted and so we did perform a bronchoscopy before the etiology was ascertained. And the lavage indicated 62% lymphocytes. And so, that has been typical for many of our patients that the initial inflammation is lymphocytic in nature. He did have lymphopenia with an absolute lymphocyte count of 1,000 per microliter and he had mild AST/ALT elevations with elevated CRP.

He did have initial normal BNP, as well as troponin as well as the normal echocardiogram throughout the course of his hospitalization. These include both formal transthoracic echocardiogram, as well as bedside critical care physician directed ultrasonography other than mild pulmonary hypertension. Next. Here are some trends in this patient's labs over the course of his ICU admission, where you can see that there were some elevations in CPK which is something that we are seeing. This particular patient peaked at around 450 and decreased but some of our patients had CPKs up in the ranges of 2 to 3,000.

His CRP was elevated and decreased over the course of his hospitalization. His lymphopenia steadily improved over the course of his hospitalization. And you can see the P/F ratio is the ratio of the PA of two to the fractional of inhaled oxygen, which is an indicator of severity of his ARDS. And the sawtooth pattern, you see there is typical for our patients who are both supine and then prone whether P to F ratio will drop as their supine for routine care before pronated, again, for their management of ARDS. Next slide.

So as I mentioned earlier, one of the things we noted about this patient was the profound weakness and myopathy that he develop through the course of his hospitalization. And that has affected our approach to our patients moving forward and minimizing neuromuscular blockade, minimizing steroids and really trying to institute early physical therapy within these patients and trying to keep the sedation lighter, so that we try to maintain their strength so that when they're ready to be extubated that they have the strength to clear the secretions cough and remain extubated. He did have a few hospital-based complications. He did develop a DVT, subsequent hematoma on anticoagulation when anticoagulation was held contralateral DVT. And it's some of the questions we've been asked about our cases is whether or not thrombosis is a common complication.

Our observations so far are anecdotal, but this is one patient who did have some significant thrombotic complications. Another thing that's interesting to point out about this particular case is that, although receiving remdesivir, Azithromycin and Hydroxychloroquine and the benefits of all these medications, I think, are still uncertain. He remained positive for COVID-19 on a retest after three weeks, and was only negative after a repeat test in the fourth week of care. Next slide. The second case that I'm presenting is a patient who had a very different clinical course all together.

This is also a community acquired case of COVID-19. He was generally healthy with well controlled asthma, hyperlipidemia and prosthetic hypertrophy. He was a very active person who had good

functional capacity. He just started developing symptoms about seven days prior to admission to the ICU. And then was seen at urgent care of four days prior to that.

He received a chest x-ray and was treated with Azithromycin for a community acquired pneumonia. On the day of admission, at the very end of February, he present to our emergency room with hypoxemia. He was placed in a high flow non-- high flow nasal cannula for oxygen treatment, and ultimately intubated within 24 hours. So at the time of his admission, he did not have a notable risk factors for COVID-19. And he tested positive two days subsequent to that.

Next slide. Here are his chest x-rays, the four days prior to admission and is seen an urgent care and treated with a course of Azithromycin. And you can see how over the course of four days, there's a significant development of bilateral airspace, opacities, absence of any significant pleural effusions, and a chest x-ray quite typical for what we've seen. This one has a bit of more of a patchy almost nodular appearance across areas of the lingula and some nodular passages have been reported in some of the other radiographic and radiological studies of COVID 19. Next slide.

Here's a CT scan that was obtained by the patient which shows very typical ground glass opacities with interlobular septal thickening and very small pleural effusions. Next slide. He was initially treated with Cefepime and vancomycin which were narrowed based on culture. Several days later, he was initially required paralysis and proning for management of his hypoxemia any ARDS as well has received lung protective ventilation. He received compassionate use of remdesivir.

He was weaned off of vasopressors by day seven, but subsequently 11 days into his hospitalization developed acute kidney injury, worsening creatinine, and developed worsening shock, as well as new onset of left ventricular dysfunction with a normal troponin. He ultimately required renal replacement therapy in the form of CRRT and by his 24th day in the hospital, he was failing his breathing trials, remained comatose, of sedation for several days. He underwent an MRI of the brain, CT of the brain and a lumbar puncture as well, all of which were negative for any specific pathology. He then continued to acutely deteriorate further. His goals of care had changed after a family conference and the patient expired into his three and a half weeks of care.

Next slide. Here the trends in his labs over the course of his hospitalization, contrasting with our other patient through the course of his hospitalization, CPK although it was mildly elevated, increased through the course of this hospitalization as did his CRP. He did present with leukopenia which was a near universal finding for all of our ICU admissions with COVID-19, which recovered briefly, but then worsened again throughout the course of this hospitalization. This patient ultimately did not die of refractory hypoxemia. Throughout the course of his hospitalization, his PF ratio is a marker for severity of his ARDS and oxygenation, gradually improved the course of his hospitalization is really other complications that were the most problematic.

Next slide. As an initial evaluation, he did receive a bronchoscopy which showed 32% lymphocytes. Again, consistent with what we have seen in our other patients who did receive bronchoscopy. It's worth noting that generally we do not do this on initial evaluation of our patients. Once it was apparent, the cause and etiology of our patients presenting with respiratory failure in ICU, we have been doing bronchoscopies when necessary to assess for or rule out infectious complications or patients who have been on the ventilator.

His initial procalcitonin is 0. 97 and he received a repeat bronchoscopy halfway through his course in the ICU to assess for the presence of pneumonia, and at that time he had negative cultures and the lavage

is mostly neutrophilic. Next slide. When he was admitted to the hospital secondary to his age and shock, he did receive a transthoracic echocardiogram which was normal. A limited echocardiogram further on his course remained normal.

And coinciding with the time that his shock again worsened and his renal function started to deteriorate. He had a new onset of global LV dysfunction without further evidence of thrombotic complications and a negative troponin, and without ST segment changes. Next slide. So I'd like to just briefly also summarize our overall experience in our ICU. These numbers are rolling numbers and pulled from our data sheet several days ago, and so are always changing.

But at this point we've admitted about 45 patients to our ICU. Slightly more than 30 of them have required mechanical ventilation. Out of that patient population, we've transferred four of them out of our center to other centers for ECMO therapy. Three of those were ultimately cannulated at their respective institutions. Out of this cohort of patients, we've extubated seven patients at the time that I made this slide and then subsequently another two so we're up to nine extubations and their ages range from 44 up to 84.

One of these extubations also includes one of the individuals that is transferred out for ECMO. That patient required both ECMO as well as renal replacement therapy, and was 44 years old. The duration of our mechanically ventilated patients in the extubated population has ranged from as little as five days up to 13, 14 days and out of this panel of patients, four of them have required renal replacement therapy. Next slide. Our general approach to care for our patients has been to intubate early once it's apparent that they're progressing rapidly.

We do use high flow nasal cannula as a bridge to intubation. We have not been using noninvasive positive pressure ventilation as a bridged intubation. We've been using early proning as well as lung protective ventilation. And based on our experience for the duration, the calculation and how weak our patients have been once they're extubated, we've been focusing on very light sedation and early physical therapy. This is included being able to get patients up to bedside, dangled their feet while they remain on LPV.

We've tried to avoid corticosteroids in general, unless there's been a clear indication such as airflow obstruction or refractory shock. We have had a remdesivir trial that's been instilled in our hospital. And so our first priority is to use therapeutics through the clinical trial that's available. Many of our patients are receiving hydroxychloroquine as well, although its benefit remains unclear. One of the things that is interesting about this particular patient population in comparison to some of the other patients that have ARDS, and respiratory failure is that the severity of their shock really is not refractory.

Most of them are managed on moderate doses of a single agent of norepinephrine and often we can wean these to fairly low doses of norepinephrine fairly early. And in line with that, these patients do not end up significantly fully positive due to the resuscitation needs. The back side of that, is that as clinicians in the ICU, we often have the opportunity to watch these patients develop ARDS, and shock come out at the back end of this where you can start to diurese them and see significant improvements in their oxygen requirements. But in the COVID-19 population, really, it's a very slow and steady process. Many of them get worse for several days after intubation because there isn't any true source control for the source of the ARDS.

And their improvement thereafter is often very slow and can take quite some time with little change from one day to the next. As I mentioned earlier, many of these patients did not have secondary bacterial

infections and so we've been discontinuing antibiotics early, as long as cultures remain negative and of the procalcitonin early on was negative. Anecdotally, I think I can recall maybe two patients who had simultaneous bacterial infections at time of it mentioned. One with haemophilus influenza and the second Klebsiella pneumonia, both of whom did have elevated procalcitonin. The other exception to the lack of secondary infections is one individual who presented with both COVID-19 as well as influenza A.

And they had an early MSSA infection. And then the other thing that we've done is early consultation to our supporting institutions in downtown Seattle for ECMO and some of our youngest and sickest patients. Next slide. And then it's the last slide.

Thanks so much Dr. Bundesmann for those really great case presentations and wonderful summary of the approach to critical care management at Evergreen. And there'll be time to address questions at the end. So moving on to our next speaker, Dr. Waleed Alhazzani, who's associate professor of medicine at McMaster University in Hamilton, Ontario, and he is the lead author of the Surviving Sepsis Campaign: Rapid Guidelines on the Management Of Critically Ill Adults with COVID-19.

Dr. Alhazzani is going to present these guidelines over to you. Thank you.

Hello, everyone. Thank you Dr. Uyeki for the kind introduction, and thanks to Dr. Bundesmann for the fantastic presentation. Next slide, please.

These are my disclosures. They're mostly intellectual, and the Chair of the GUIDE Group in which we support clinical practice guidelines. I'm also a member of the GRADE Working Group. Again, these presentations do not represent the official opinion of the CDC. Next slide please.

I would like to start by thanking my colleagues on the panel who did a fantastic job to make these guidelines happen in a timely manner, and it's a privilege to be presenting on their behalf. Next slide please. OK, before we dive in into the recommendation, I want to take you quickly through the process of developing those recommendations. So this slide summarizes in a nutshell the steps from introducing the PICO question for each of the recommendations. I think we had more than 50 PICO questions.

We did a rapid systematic review for each of those questions, identified the relevant evidence. As you can imagine, given the recent onset of the disease, there isn't much high quality evidence available that is direct to COVID-19. So you relied on both not only direct evidence, but also indirect evidence from previous ARDS, you know, Corona viruses and shock literature. We did attempt summarizing the evidence when appropriate. If the evidence is already summarized, we use the great methodology to assess the certainty in the evidence.

The panel look at these evidence tables, issue recommendations, and finalize writing the manuscript. Also, before I dive in into the recommendations, I think we should all agree on the terminology. So whenever the desirable consequences of an intervention clearly outweighs the undesirable consequences, next slide please, we issue a strong recommendation favoring that intervention. So, this is-- these are the situations where there is a strong recommendation. Next slide.

However, when the desirable consequences of an intervention probably outweighs or the distinction is not very clear, then we issue a weak recommendation. Next slide. And there are implications of weak recommendations versus a strong recommendation. I'm going to go through quickly in the next few slides. Next.

So for patients, what does a strong recommendation mean? It means that most individuals who are faced in this situation would follow the recommended course of action or the recommendation, and only the minority would not as opposed to a weak recommendation were certainly majority or many would follow the course of action. However, there will be many who would not say, and will say no thank you to that intervention. Next. Similarly, for clinicians, the implications of a strong recommendation means, you know, you should must do it or must not do it depending on the context of the recommendation. If you don't do it, then you have to have a really good reason why as opposed to a weak recommendation where there is a slight preference for the intervention.

And you probably should follow it, but there will be situations where the intervention might not be applicable, or that patient values a preferences or resources might have an implication of that recommendation. So it's a clear-- although both are called recommendations, the implications for practice are different. Next, our policymakers level a strong recommendation could serve as a policy in many institutions or many situations. However, a weak recommendation is unlikely to be a fixed policy and the policies will vary according to institutions. Next.

OK. We divided our guideline into several sections, including infection control, hemodynamic and ventilator support and therapy. For the infection and control section, there's excellent guidance out there from CDC and WHO, so we did not want to reinvent the wheel and we focused mostly on questions that we thought are very relevant to healthcare workers in the ICU. And the general themes that we looked at that dividing the procedure risk, aerosol versus nonaerosol generating procedures and also focusing on, you know, when to use negative pressure rooms versus regular rooms and what kind of masks to use. Next.

We did do a systematic review looking what's available out there. We finally identified several reviews. Most recent was published many years ago. But again, not surprisingly, this review shows that endotracheal intubation manual or sorry, manipulation of the BiPAP mask, or conducting CPR, doing tracheostomies are associated with the highest risk of aerosolization and disease transmission. Next.

So keeping that in mind, when clinicians or healthcare workers in the ICU performing an aerosol generating procedures, we issued a best practice statement which is a strong recommendation, favoring a fitted respirator mask which is an N95 respirator or FFP2 or equivalent like popper, as opposed to just a regular surgical mask because of the high risk of the procedure and a high risk of disease transmission. Next. However, in situations where healthcare workers are providing care for nonventilated COVID-19 patients who don't-- who are not undergoing any aerosol generating procedures or those who are intubated, and again, not going under an aerosol generating procedure, we issued a suggestion or a weak recommendation for using surgical or medical masks as opposed to a fitted respirator masks. And again, this recommendation will vary according to the context and situations where PPEs is not a problem and abundantly available and I can't think of any to be honest, maybe the institution will lead more towards aggressive measures. However, given the global shortage of PPEs, it seems that it's reasonable to use surgical medical mask, and we also looked at the evidence I'm going to discuss on the next couple of slides.

Next please. So, we did conduct our own systematic review, we identified several RCTs that looked at specifically N95 versus surgical or what is also known as medical masks. And we did attempt to pull the estimates across those studies. So if you look at laboratory confirmed influenza infection, it doesn't seem that 95 is better. Again, the confidence interval is pretty wide, so the certainty and the evidence is low and this is from completely indirect evidence and influenza patients.

Next please. Also, lab confirmed respiratory infection was not significantly different between the two groups. Next, please. Influenza like illness, although it seems that N95 reduces that risk, the confidence intervals still across the line of no effect. So, there is still some uncertainty that does not mean that, you know, that they are both equivalent.

It just means that we have low certainty that there-- that the difference is nonsignificant. So, it seems that medical surgical mask is a reasonable alternative if there is no aerosol generating procedures. Next please. The next thing we focused on those patients that present with hypoxia, so, what are the oxygen targets? Next. And as you can see in this U-shaped curve, it seems that both extremes of oxygen saturation could be harmful to patients.

From recent evidence that seems that saturations are hyperoxia or hypoxemia could be associated with increased risk of harm. Therefore, we issued a recommendation to target upper limit of oxygen saturation not higher than 96%. Next. We issued a suggestion to start supplemental oxygen if the saturation is less than 92%, trying to accommodate the recent published evidence. Next, but we also issued a strong recommendation for patients who are hypoxemic with an oxygen saturation that is less than 90% to start oxygen supplementation.

I have to say that these recommendations apply to patients who don't have COPD or chronic obstructive pulmonary disease or those in home oxygen. So those are not included in the recommendation. Next, please. And again, this is from a recent systematic review that were published a couple of years ago looking at RCTs from acutely-- patients with acutely-- were acutely ill in the hospital. And as you can see, there is a linear relationship between the increase and a percentage point separation between both arms and risk of death.

Next please. OK, so what to do with these patients and again, this is-- these recommendations are controversial and they're subject to several contexts. So in patients who-- with COVID-19 who present with acute hypoxia despite being on conventional oxygen therapy, we issued a suggestion for using high flow nasal cannula over continuing conventional oxygen therapy. And this is based on indirect evidence suggesting that high flow nasal cannula work for patients with acute hypoxemia. However, there's a caveat here that we are not sure if high flow oxygen increases the risk of disease transmission therefore, you know, you-- people should follow their local institution policies if they're using high flow nasal cannula in terms of infection control.

Next please. We also suggest using high flow nasal cannula over noninvasive ventilation for a couple of reasons. Noninvasive ventilation is associated with aerosolization as we know also from previous anecdotes and Corona viruses the failure rate was higher in patients who received noninvasive ventilation. Next. If for instance, a high flow nasal cannula is not available, and there is no emergent indication for intubation, and people have enough resources to perform a non-aerosolizing procedure like an invasive ventilation.

It's not unreasonable, clinicians have used it recently and it's-- we made a suggestion for a trial of noninvasive ventilation CPAP or, you know, BiPAP less preferably, and with close monitoring at short intervals, and for any worsening respiratory failure. Again institutions, as I mentioned before, the implication of this recommendation will differ according to institutions. For example, at my institution, we don't use noninvasive ventilation in those patients. Next please. We did not make a recommendation helmet BiPAPs or helmet noninvasive ventilation or CPAP.

And because there is insufficient evidence for safety in this disease, however, colleagues have used it, especially in Europe. Next. And probably all aware of the single RCT have been published showed reduction and need of intubation and patients who received helmets noninvasive ventilation in patients with the ARDS so this is not in COVID population. Next. Endotracheal intubation again, it's a subject of debate when to do it.

However we made a strong recommendation, so as you can see the theme in the ventilation section is mostly weak recommendations, the only strong recommendation was to perform endotracheal intubation by a person who's experienced area management to minimize the number of attempt and hopefully minimize risk of transmission. Next. We also suggest using a video guided laryngoscopy, and this is for two reasons, a previous studies in non-COVID patients have showed a lower failure rate with video guide laryngoscopy but also you can maximize the distance between the provider and the patient airway and hopefully reducing the risk of transmission. Again, this is subject to resources and availability of equipment. So if it's available, it's better to be used.

Next. This slide summarizes the flow of the recommendations and as you can see, at several occasions, we always assess the patient for need of endotracheal intubation. And I have to say that this slide is specifically will be highly affected by the availability of resources and infection control measures. If there are no issues with that, then a trial of high flow nasal cannula or even noninvasive ventilation, it's not unreasonable. However, that's not-- what's not acceptable is just to leave patients on these interventions and not assess them frequently.

If that's not a possibility, then maybe it's safer to intubate the patient rather than wait until they develop crisis and then intubate in an uncontrolled setting or an emergency situation. So again, it's subject to clinical decision. It's meant as a guidance and there is a lot of recommendations here in yellow which means consider doing this if applicable. Next, please. OK, the next several recommendations will focus on acute respiratory distress syndrome, so they are not applicable to patients with COVID-19 pneumonia without ARDS.

So specific for those patients who develop ARDS. Next. Similar to general ARDS management, these recommendations come from general critical care literature. We recommend protective lung ventilation with targeting low tidal volumes 4 to 8 mLs per kilo and targeting plateau pressures not higher than 30 centimeter of water. Next.

Again, PEEP levels a little bit tricky, if the patient is PEEP responsive, then they probably should receive higher PEEP. However, those who are not PEEP responsive, increasing the PEEP could affect the cardiac output. Having said that, and those with full ARDS with some recruitable lung then, you know, talked-- we said we made-- a weak recommendation to target higher PEEP. Next. Also similar to my other colleagues have mentioned we also made a weak recommendation suggesting to people using conservative fluid strategy over liberal fluid strategy.

Next. OK, prone ventilation, proning is a simple intervention, especially in trained-- when healthcare workers are trained to do it. And it seems to be effective in general-- generally in patients with moderate to severe ARDS, especially those with severe ARDS. So, we issued a suggestion or weak recommendation to prone patients for at least 12 to 16 hours, as proning them for less than duration have shown not to be that beneficial. Next.

What about neuromuscular blockade? Again, we try to incorporate recent evidence from the last trial and the previous body of literature, mostly from the French studies. Next. And by looking at the total

body of evidence, again in the patient population with ARDS, not specifically with COVID we issued a weak recommendation or a suggestion to use intermittent boluses of neuromuscular blocking agents when needed over starting continuous infusion on everybody. The aim is to facilitate protective lung ventilation. Next.

However, in cases where there's persistent ventilator dyssynchrony despite these boluses or requirements for ongoing deep sedation to facilitate protective lung ventilation, or patient were prone, or have consistently have higher pressures then it seems to be reasonable to put those patients on a continuous a neuromuscular blocking agent infusion. The most commonly studied medication is cisatracurium for 48 hours, so rather be reserved for those who are really sick and which initial measures did not work, then it's not unreasonable to start in infusion of this very specific population. Next. Corticosteroids very controversial. So I'll try to walk you through the rationale of why and how we did end up with these recommendations.

Next slide, please. OK, so looking at steroids or corticosteroid use in ARDS patient. So again, this is a body of evidence not in COVID-19 patients, but it seems there are seven RCTs at least or more than that, that looked at the use of corticosteroids in ARDS and it seems that there is a consistent-- at least the pooled estimate suggests reduction in mortality. Next. And also reduce the duration of mechanical ventilation.

Again, these studies are subject to bias as several of them are not blinded. So an outcome like duration of mechanical ventilation is high subject to both, but it seems that on average reduce duration of mechanical ventilation by close to five days. Next, please. OK, what about using steroids for viral ARDS. We did look at all observational studies.

We only found few of them. When you pull the results together, it's very heterogeneous, really no clear effect. And it's inconclusive. I can't really make any judgment based on this. Next please.

Recently, you know, a small retrospective study from China showed that patients with COVID-19 pneumonia respiratory failure, specifically, those with bad ARDS receive methylprednisolone, I believe that those uses about 60 milligrams daily had lower mortality. But again, these are observational studies, so the only direct evidence that we have at the time of guideline publication was this study. Next. So trying to put everything together, we have indirect evidence from ARDS patients show and suggesting reduction in mortality. We have some direct evidence in COVI-19 patient suggesting maybe there is reduction in mortality.

So we issued a weak recommendation to using systemic corticosteroids, over not using corticosteroids in patients with ARDS. I will even say in those with moderate-- at least moderate to ARDS. I also have to disclose that this was a very contentious recommendation across the panel. This is why it's weak. And several experts on the panel it preferred that we don't say-- we don't make a recommendation here.

Next. What about the evidence for viral pneumonia? Again, this is an up to date summary of the literature. If you look at the influenza literature in the upper part of this forest plot, there's an increased risk of death and those who receive steroids again, observational studies, when you looked at specifically of Corona viruses, the evidence was all over the place. It's really difficult to say anything. So there's a signal towards harm with influenza.

The signal is not clear for Corona viruses. Next please. This have led to a suggestion against using steroids routinely in patients without ARDS. You have somebody with COVID-19 with respiratory

failure or somebody in the ICU and this patient unlikely to benefit from steroids, there's potential for harm, therefore, a conditional recommendation against the use of steroids. Next.

I'm not going to go through the slide. Hopefully you have the slides available to you. Again, just to put into context, the different interventions that we talked about and the strength of recommendation. Next. Antibiotics, again, a controversial recommendation.

However, in those who are sick in the ICU with COVID-19 respiratory failure, we made a weak recommendation to use empiric antibiotics compared to not using empiric antibiotics, but with clear remarks saying that this should be assessed in daily basis and de-escalation once, you know, concern about bacterial infection is out of the picture, these antibiotics should be stopped. Now reports are coming saying that community acquired infections are not so common. However, those who stay in the hospital they're at risk of developing nosocomial infections. So clinicians should use their best judgment on when to use antibiotics versus not, so it shouldn't be like a routine thing to do. Next.

Again, due to a lack of evidence and lack of success with these interventions in previous viral studies, we issued suggestion against the routine use, so for immunoglobulins convalescent plasma and antivirus like Kaletra based on the recent New England Journal of Medicine paper, although that study specifically was underpowered to, you know, make any conclusions so these agents should be used, preferably under the context of research or clinical trials. Next. There was insufficient evidence to make any recommendations for other antiviral agents, antimalaria agents or immune modulators. So, we just discussed what we know about the current evidence or even the in-vitro studies but made no recommendations. I have to say these guidelines would be living guidelines.

So we will be updating our recommendations rapidly as new evidence emerge. Next, a couple of last slides in hemodynamic supports, there are several of recommendations. And there is managements probably similar to patient who present with shock, you have to make sure they don't have a cardiogenic component. If they have pure septic shock, we made a conditional recommendation or a weak recommendation favoring conservative fluid strategy over liberal fluid strategy, as most of these patients will have respiratory component as well, and flooding them with fluid might not be a good idea. Next.

We also made a weak recommendation for using low-dose corticosteroids in patients with shock. So patients who have COVID-19 shock, but there is at least indirect evidence suggesting maybe some benefit of you know, hydrocortisone less than or 200 milligrams a day, either as a continuous infusion has been used in some studies or intermittent dosing. Next. It's my last slide. So special thanks to the guideline panelists and methodologist, the sponsoring societies and colleagues around the world who are caring for COVID-19 patients.

Thank you.

Thank you so much to our presenters for providing our audience with such useful information on this rapidly evolving pandemic. We appreciate your time and value your clinical insights on this matter. We will now go into our Q&A session. Captain Uyeki would you be so kind as to moderate our Q&A session today?

Yes, thanks so much. Special thanks to Dr. Bundesmann for great presentation and also wonderful overview of the surviving sepsis campaign guidelines from Dr. Alhazzani. Just to start off the questions, just for Dr.

Bundesmann, you mentioned in your presentation, the duration of mechanical ventilation and those that you have extubated to be about five to 13 days, just wondering in those that haven't been extubated, how long are you seeing patients on mechanical ventilation? And then are you seeing any differences in the duration of mechanical ventilation and those who are much older elderly adults versus nonelderly patients.

There are longest patients that underwent mechanical ventilation and ultimately passed away were on event for more than three weeks. One of the patients three started to get into discussions regarding whether or not to trach this person or not, ultimately he deteriorated clinically and withdrew care. Both of those patients were one was in their mid 60s, other one was more than 70. So that's right within the mean age of our populations that were described in the both the JAMA and New England Journal of Medicine papers.

Thanks very much, Dr. Alhazzani in your experience, or what is the duration of mechanical ventilation that you're seeing in your patients, and any differences in elderly versus nonelderly?

That's a great question. So in our institution, we're lucky we didn't get hit bad with, you know, we expect the peak within three to four weeks. But, however, the patient we've seen, seems to me that disease is a grumbling disease is not, you know, some deteriorate quickly, so it's highly variable. But most of the patient we have in our unit got ventilated for no less than five to seven days. Some-- we have still a couple of patients who have been intubated now for close to two weeks.

Yep. Thanks very much. And then Dr. Bundesmann, you mentioned sort of your bridging strategy with high flow nasal cannula and kind of avoiding noninvasive and then going to mechanical ventilation. Do you have any thoughts about, you know, in general going towards early intubation before trying noninvasive ventilation strategies?

Well, with our institution with the use of high flow nasal cannula, somebody is in a situation where we feel like they're feeling high flow intubation becomes more of an emergent process and given the risk of transmission of aerosolization procedures, you know, trying to delay that process any further with hoping to rescue them with noninvasive, I think just increases risk both to the patient as well as the provider team when things become more urgent on the fail that as a rescue therapy for high flow. And once people start to deteriorate in our experiences they tend to deteriorate rather quickly, and so getting them intubated on mechanical ventilation leads to a more controlled situation for everybody.

And Dr. Alhazzani do you have-- does your institution have any strategies in early intubation or not?

Yes. I will just take a step back. So, this is a very important question to address. There are two sides of the equation here. So one side is, you know, you have to minimize risk of transmission of disease to healthcare worker, and make sure we deal with this because of the rapidity of deterioration of the disease, and maybe preferably intubate patients.

The downside here is you probably going to intubate patients who could have, you know, improved without the need of intubation. The issue is, we don't have good predictive tools to tell us who might do well without intubation and who might not, so clinical intuition and clinical assessment is extremely important. But intubation itself is not a benign procedure. It's also associated with its own risk of aerosolization. In fact, there's odds ratio according to that paper that I quoted was one of the highest in terms of procedures, you know, causing disease transmission.

So it's not a benign procedure, it could be harmful for some patients however it has its own advantages. And the other side delaying intubation and relying on other measures to avoid it at all costs might also have its downsides. Again, as have been mentioned, doing-- you know, a patient's can crash really quickly and it seems to be consistent message across you know, colleagues in China, colleagues in Italy and the States and Europe, seeing the same thing. When patient deteriorate, the utility rates were rapidly. So the key is to find that, you know, it would be nice to have some studies to help predict who are the patients who are not going to do well and guide practice.

In our institution. we allow to use high flow nasal cannula in negative pressure rooms with airborne precautions. We strongly advise not to use NIV because the risk of aerosolization. Colleagues in Europe have used, and even in China, have used NIV a lot. And there are, you know, anecdotes of patients who have avoided intubation with just simple positive pressure.

So at the moment, I don't think we have a clear answer. People have to balance the downsides and the potential benefits for each intervention. This is why the recommendations were weak in our guideline.

Yup. Thanks so much. Dr. Bundesmann, in your experience, as well as those of your colleagues or other colleagues in the Seattle area, what you've been hearing around the country, what-- how frequent is reintubation during the same hospital admission in your critical ill patients who managed to get extubated. Are you experiencing that? Are you hearing about re-intubation being required?

Yeah. It's a really important question. I-- anecdotally, we are hearing from other institutions as well that a fair number of their patients that get extubated are being reintubated. We did have a stretch where we had to reintubate several of our extubated patients. And, you know, the question is, why is this happening? You know, one potential explanation that we see is that a lot of these patients are spending a lot of time with pretty high grade fevers.

They're appearing to be quite weak. Even people who generally seem to be fairly strong prior to the intubation institution, mechanical ventilation appear to be having difficulty, you know, clearing mono secretions once extubated. And so I think this is a component that may affect how we approach the problem. If it appears that with this disease that people have high rates of reintubation, just because the generalized weakness after their duration of intubation, it may change how we approach assessment of extubation. You know, generally, we combine our sedation vacations with a daily push for trial.

And if somebody appears otherwise ready to be extubated after, you know, push for trial on two hours, then we extubated them. And if we become slightly more cautious about doing this, you know, some of our more recent extubation, we've-- while the patients are pushed for trial, we've tried to see that they also tolerate additional physical therapy, you know, dangling their feet and doing more activity to see if they're strong enough. And the downside of this, of course, is that we may wait too long to extubate patients, and then are facing consequences of an increased risk of pneumonia infection and delayed extubation. So out of the patients that we have extubated, we had reintubated two of them. Both of them did ultimately get reextubated and have remained extubated.

So that's two out of, I think, nine patients, I mentioned, which is, you know, slightly higher than I think the reintubation rate in many of the published studies, but it's a small population of patients so far.

Thanks so much. Dr. Alhazzani, do you have any comments or thoughts on that issue of reintubation?

No. I think the numbers in our institution is still small to have an idea like to give you a local experience. So Michael, you know, answered the question fantastically. We all learned from his answer, great.

And then Dr. Bundesmann, what are-- in these patients who are not surviving, what are they actually dying of? Are they dying of refractory hypoxemia? Are they dying of multi-organ failure, septic shock? What is actually the cause of death in these patients?

Yeah. In our population, we've seen a mix of things. Some of them have developed just refractory multi-organ failure such as the second patient that I presented today after three and a half weeks plus worsening shock and renal failure and ultimately transition to withdraw of life support and comfort care measures. There are not many patients that we've had really they've had refractory hypoxemia. We did have the transfer for out-- for ECMO.

And so I think, you know, that population clearly exists. But there has been a mix of things that have caused them to ultimately pass. Some of the patients, there was a withdrawal of care because their baseline functional status-- and then having a prolonged course was filled with the likelihood of meaningful extubation for these patients wasn't going to be high. So, some of them had withdrawal of care early into their course, just based on their histories and comorbidities prior to coming to the ICU. Otherwise, we did also have a population of patients who had fairly precipitous cardiac arrest patients who otherwise being supported on minimal norepinephrine, moderate vent settings who would develop bradycardic arrests and develop new onset of LV function abnormalities on echocardiogram afterwards.

Now, this was not reported, I think, in the New England Journal Medicine case series that was just published a day ago. So I think we have to wait and see whether or not this is a broader finding with the COVID-19 patients. But there were a certain fraction of our patients who appeared to have new onset cardiomyopathy as part of their disease process and cardiac arrest. And they otherwise have been stable from their shock standpoint and from their ARDS standpoint.

Yup. Thanks so much. And Dr. Alhazzani, could you go into more details about what you mean by a conservative fluid strategy? And is there a role of daily diuresis?

Fantastic question. If you read the guideline document, you'll notice that we did not provide guidance on what it means because different studies use different algorithms, different interventions. However, the common theme is minimize infusions of fluids that are not necessary. Try to target a neutral fluid balance or even a little bit negative fluid balance. Using diuresis, you know, with proper volume assessment of the patient might not be a bad idea.

Some of the RCTs that have been, you know, published have used diuresis as a component. But it would be very difficult to say, you know, this is exactly what clinicians need to do, one, two, three. Clinicians have to assess their volume status, avoid hypervolemia at all cost and try to target neutral fluid balance. If that requires-- if minimizing fluid is enough, that's great. If you need to give a little bit of diuretics, you can give it with a close monitoring of electrolytes and kidney functions.

Yup. Thanks. And Dr. Bundesmann, I think you were talking a little bit about keeping patients on the dry side. Did you have anything to add to this issue of conservative fluid strategy?

Yeah. I think one of the thing that I observe, that our group has observed, a lot of these patients with their high fevers also have a lot of insensible losses. And so, as we go through and try to track people's

ins and outs and daily weights, we don't really get too far with attempting to diurese any of these patients aggressively. We're trying to keep them essentially even. But recognizing that a lot of them have more insensible losses than many of the other patients who are used to being on ICU with their ongoing high fevers for days after days.

Yup, thanks so much. And then Dr. Bundesmann for the intensivists that are listening in, could you go into more details about how your ventilatory management is for moderate to severe ARDS in these COVID-19 patients, P plateau pressure, tidal volume, et cetera, FiO2?

Our general approach for ventilation is a fairly, I think, standard approach, I think, based on the ARMA trials and the LPV trials from the ARDSnet. They've been well polished and then followed. Essentially when patients are intubated, if their P/F ratios after they've had some opportunity to recruit are less than 150, then we tend to proceed with proning, initially with a long period of time, usually 16 hours. And then continuing onward until their P/F ratios on lungs show sufficient improvement. Our PEEP letter is based on the ARMA trials.

And so, typical PEEPs for our patients, when they're the more severe patients really haven't been at the very high range. They haven't required that or needed that. A lot of our patients are in a PEEP from, you know, 10 to 14, and their driving pressures. That's the difference between plateau and PEEP, are typically in a range of 8 to 12 for our patients. I guess anecdotally, if I were to compare these patients to some of our severe influenza patients, my experience with those patients with ARDS, they had much stiffer tighter lungs with higher driving pressures and difficulty maintaining the goals of LPV, which is to maintain a plateau less than 30 tidal volumes, you know, less than 6 ml per kg.

Whereas most of these patients, we've been able to maintain within the goals of lung protective ventilation and with institution of proning.

Yup, thanks so much. Dr. Alhazzani, did you have any additional comments on that?

Yes. It's a great explanation and I agree. But there have been at least some anecdotes, and from colleagues that observed less ARDS or classical ARDS pattern. So, you know, some colleagues have reported that those patients have actually good lung compliance. So, you know, I would-- if-- I'd say to clinicians, you know, just, you know, cranking up the PEEP might not be always the solution.

Some patient actually may do well with just, you know, lower PEEP. So you have to have a-- you either follow the published protocols of the ARDS trial. Or, if you're-- you know, you have enough resources, you can always test the optimal PEEP. In our center, we have enough experience with ARDS, so we have enough resources. So we always test the optimal PEEP targets.

Just a word of caution that, you know, cracking the PEEP all the time might not be the answer in those patients. And as Michael mentioned, some of those patients, they present with just pneumonia and not necessarily ARDS, or your classic like stiff, you know, lungs that are very difficult to ventilate or-- so that seems to be one of the themes. Although some pathology, you know, post mortem pathology studies have shown that these patients may actually have, you know, classical ARDS features at the molecular level. So a clinician have to make this distinction when they treat the patient. Thanks so much.

And Dr. Bundesmann, you mentioned proning, prone positioning, in your-- you and your colleagues' experience, do you think without doing a trial, but do you think that the proning is really benefiting these patients? Are you really seeing some tangible-- some benefit?

Yeah. I think it's a difficult question to answer specifically for this patient population. So, you know, proning has been shown to, you know, reduce ventilator free days in the general ARDS population and improve mortality. What we see face up in our ICU, of course, is improved oxygenation. But we also know improved oxygenation doesn't always correlate with less lung injury and reduced ventilator time.

It certainly has allowed us to minimize the usage of neuromuscular blockade. And in that sense, I think it's been beneficial and trying to keep our patients as awake as possible. You know, I think one important question is whether or not prone patients need to be deeply sedated. Some of our patients we've been able to prone where they're actually able to assist us and turning and some of them have one of our intensivist managed to get patient to do push ups well prone just to maintain their physical capacity to get off the ventilator, and that patient is able to be extubated after six days. So, you know, I think that's obviously an extreme anecdotal example.

But if we found that it really has allowed us to avoid, I think, some other interventions that may prolong intubation in terms of, you know, deeper sedation and neuromuscular blockade. But, you know, I don't-- it hasn't been tested in this population yet, right. We're borrowing from the ARDS literature in general.

Yeah. Thanks so much. So, Dr. Alhazzani, you know, you mentioned how controversial the issue of corticosteroids are in particularly high dose corticosteroids, so in the published literature from China, we know that also in the Chinese national guidelines now in its seventh edition, but all along, there's been sort of standard use and very high use of-- high dose Methylprednisolone, one to two milligrams per kilo per day. And the question is if there's a weak recommendation for corticosteroids and the two small published ICU case series from the Seattle area, you know, systemic corticosteroids were not being given, at least for treatment of COVID-19.

What do you think the role might be of low dose corticosteroids, such as hydrocortisone at sort of using the surviving sepsis campaign dosing in patients with ARDS without septic shock or other low dose corticosteroids?

It's a great question. I think the answer is we don't know. We are again borrowing from indirect evidence to extrapolate to see if the sickest people or the highest risk of death, those with moderate to severe ARDS would patients being at that level of sickness and advanced disease would benefit from an intervention that's shown to be probably beneficial and ARDS not specifically from viral geology. So that's where the weak recommendation comes from. The-- we stayed silent on the dosing because we really don't know.

My general feeling is if you use steroids, try to avoid, as you mentioned, high dose steroids as much as possible. Definitely in my mind, two milligrams per kg is pretty high. If I throw a number there, you know, I wouldn't go above 50, 60. But again, that's my own general, you know, practice, it is not evidence-based. The studies in the ARDS population used valuable dosing.

Most recent study, used Dexamethasone at 20 milligrams, so moderate dosing. But again, clinicians if they start steroids, they should monitor the patient, you know, because we know may increase vital shedding, replication of the virus, so we still have uncertainty. The good news is there are ongoing trials, that testing steroids, so we will have a more definitive answer hopefully soon.

Yeah. Thanks so much. Do you think that the use of high dose Methylprednisolone in the critically ill patients in China has contributed or might be associated with their very high frequency of ventilator associated pneumonia anecdotally in both what's been published, very high frequency of hospital

acquired infections? And just wondering your thoughts on what the contribution of high dose Methylprednisolone might be to that.

But it is one of the plausible explanations that, you know, immunosuppressive agents at higher dosing could increase the risk of secondary bacterial infection. But again, you know, we can only show association not causality with looking at observational studies. At least, again, an indirect ARDS, you know, generally in our population, there were shorter duration of mechanical ventilation, if it gets to it, whether that happens. In COVID-19 population, we'll present with your atypically ARDS, nobody knows. But shorter duration of mechanical ventilation could translate, at least from that meta-analysis that we did to less infections if you give steroids.

But it's completely up in the air. I don't think anybody knows. It's reasonable assumption. I think at this stage, if clinicians avoid giving high dose steroids, even in the sickest patients, I think it's absolutely justified in my own personal opinion.

Yeah. Thanks so much. And one of the points you made about the surviving sepsis campaign guidelines is, you know, recommendation for antibiotics at admission. But certainly if they're going to be used to evaluate on a daily basis and deescalate or stop a bacterial infection if there's no evidence, if it's not-- no longer suspected. And one of the differences is, you know, again in the Dr.

Bundesmann's presentations and in the published small published case series from the US, really not much in the way of hospital acquired infections, which seems to have been reported from China. And I don't know if either of you wanted to comment, just any more about antibiotics and the issue of community versus hospital acquired infections in the critically ill.

Within our population of patients, so far, it's been quite rare for us to have hospital acquired infections within our ventilated patients with COVID-19. You know, again, it's hard to be certain about the causation of that is whether or not it's our avoidance of use of steroids or for other reasons, our patient populations are different. I don't think all-- now, I think more of a prospective study will help us figure that out. But for our population so far, additional pneumonias, you know, urinary tract and mind-related infections have been quite rare for us, even though some of our patients have been on the vent for up to three weeks.

I think it would be a context specific. I think there will be variation and secondary infections depending on where, you know, which data you look at, depending on which measures are taking, how busy the institution is, the volume of patients, et cetera. But also remember in the Chinese study, many patients used-- received, you know, off label medications. Some of them are immunosuppressive agents, and patients used even antibiotics for a prolonged period of time. So, you know, all these combined could actually, you know, explain why this population had a higher risk of infection.

In fact, we are planning to look at these recommendations again, maybe update the current recommendation with the panel. But I think-- and I'm just now looking in retrospect, we probably should have issued a strong recommendation for, you know, daily assessment like a best practice statement. So just I want to emphasize that if a clinician start antibiotic empirically because they have a dense consolidation, leukocytosis patient look-- they may have a bacterial infection, you start it. You have to assess antibiotics daily because it's not a benign intervention either.

Thanks so much. We're starting to hear uncommon, you know, but sporadic reports of potential neurologic complications, such as encephalopathy, or encephalitis. And I wanted to ask Dr.

Bundesmann if you had-- and your colleagues had noted any neurologic, potential neurologic complications of COVID-19.

We had a number of patients who had prolonged ventilation and oxidation for many days, enough time that we would have expected to clear any sedatives even though they're getting sedation interruption on a daily basis leading up to that. And so, the question did occur to us whether or not there will be a virus related either infection or encephalopathy or encephalitis. These patients did undergo CT imaging did not show any acute changes. One of them underwent an MRI and both of them underwent a lumbar punctures. And either of those showed any direct evidence of encephalitis.

And I think there are a lot of things that can contribute to encephalopathy in the ICU not just the COVID-19. So I think it's difficult to ascertain whether or not there's anything else related to COVID-19 versus a lot of things that happen in the course of a prolonged ICU admission. But we haven't seen anything specific that we can ascribe to COVID-19 infection in these patients.

Yup. Thanks. And then, you know, a lot of these patients that admission have mild to moderate thrombocytopenia, but some of these patients develop a thrombocytosis. And just wondering if Dr. Bundesmann if you wanted to comment a little-- any more on the issue of thrombotic events as a complication, either during the hospital course or after hospital discharge, and the issue about whether anticoagulation is something that-- in some patients should be considered with thrombocytosis.

So all of our patients are on a prophylactic dose of a low molecular weight heparin. They are not on full anticoagulation. Out of the cohort of patients that we've had, we've had two clear thrombotic complications. One, a pulmonary-- actually two DVTs essentially, which in the course of a prolonged ICU hospitalization-- I'm not sure if those rates are above what would be expected elsewhere. The other anecdotal sort of thing that we had noticed is one of the patients receiving renal replacement therapy really just consistently kept cutting off the CRT machine which didn't abate until even on heparin and they were actually switched to Argatroban, which appear to solve the problem.

Again, I don't know that these numbers are sufficient to, you know, report that this is really a finding in these patients. But those are sort of our experience in our ICU.

Dr. Alhazzani, do you have any comments about thrombosis or an anticoagulation?

Yup. From a guideline perspective, I don't think anybody at the moment could, you know, make a recommendation to anticoagulate those patients at a spec. There are hints as mentioned, maybe these-- some subset of patients are thrombogenic. We know that those with high D-dimer levels that are extremely high, you know, which could be related to the infection, but also could be related to microthrombosis as well, do worse. But until more evidence is available, I don't think, you know, we can say, you know, anticoagulate those patients.

I think at the moment, just follow what is recommended for the general critically ill patient which is DVT prophylaxis. Unless we're talking about platelet counts that are, you know, extremely high, then it's a different story.

I agree with that.

Dr. Bundesmann, do you-- in your experience, have you found any benefit of inhaled nitric oxide or other vasodilators in any of the COVID-19 patients?

The use of inhaled vasodilators either inhaled nitric oxide or what we use in our institutions inhaled epoprostenol can be helpful as a rescue therapy when patients are hypoxic. Despite proning, there's really no evidence that these interventions really change outcomes as far as I'm aware. And, you know, proning takes additional manpower, person power to get people proned and flipped. And there are times when our ICU's resources were stretched where we felt it was necessary to consider inhaled epoprostenol for some patients, or otherwise stable instead of proning. From a resource standpoint, we had to make those decisions, but otherwise our usage of epoprostenol was essentially as a salvage for patients who are hypoxic despite proning initially.

Dr. Alhazzani, any additional comments?

Yup. So in our guidelines, we actually recommended against the routine use of those. And as Michael mentioned, and in the context, whereas it uses a rescue therapy, if people use it, they have to be aware of a few things. A, if it doesn't work quickly, you have to stop it or taper quickly because there's a risk of rebound. Pulmonary vasoconstriction or worsening hypoxia.

B, if you-- in our institution for example, we have Flolan and the issue of clotting the filter and healthcare workers coming in and out to change the filter and exposing them to the risk unnecessary risk as well should be always balanced and the equation also the issue of availability of these medications. And lastly, you know, the evidence shows only improved oxygenation. If you use it routinely, or as a rescue therapy, people are desperate and patients are not doing well, you could use as a temporizing measure to, you know, for the next step like using extracorporeal life support or proning.

Great. I think we have time for just one last question here. And I'll kind of throw a couple things together. And so, as you both know, there's some clinicians are participating in clinical trials of different host directed therapeutics, including IL-6 receptor blockers, but there's also sort of uncontrolled use, and some clinicians are measuring cytokines and sort of using that to guide their therapy of IL-6 receptors. And I know surviving sepsis campaign guidelines can't make any recommendations.

I don't know, Dr. Bundesmann, do you have any thoughts about the use of-- some of these host-directed therapies in the absence of data? And also, you know, combinations of different investigational agents, including Hydroxychloroquine-- and I think you mentioned, one of your patients was on that. Do you have any thoughts about use of these investigational agents outside of a clinical trial? Any benefit? Yeah.

Well, I'll start with IL-6 directed agents. And I think that they come with some interesting promise of their benefits. But I don't think that anybody's shown this yet. And I think that they really should be used within clinical trial base, especially on the risks of infection. We have not to used any anti-IL-6 agents within our institution for our patients.

I do know that some of ours that were transferred out for ECMO did ultimately receive an anti-IL-6 agent. Our institution will be starting a Tocilizumab trial shortly, which I think is really what's needed to answer some of these questions. But in the absence of such data, I think it's best to, I think, avoid agents that can have potential significant side effects such as infection, immune suppression in this patient population. In regards to Hydroxychloroquine, I think that this is also an agent where I think a lot of people, I think, on balance that they consider what they think that both the risks and the benefits are. I think a lot of people in the lack of proven agents that we can use in COVID-19, I think are reaching for Hydroxychloroquine and as a potential option under the thoughts that its risks are low.

I think we really don't know in our patient population yet. My preference has been to avoid these agents as well in the absence of prospective data. But there's a lot of variety on that. And a good number of our patients are being placed on Hydroxychloroquine. At least the most sick individuals in the ICU, both in our institution as well as regional institutions, I think, remain somewhat guarded in the usage of these agents since there's not enough prospective data to utilize them.

I do worry about potential side effects in the long term. Hydroxychloroquine has a half life of 40 days and may potentially effect-- there are some case reports of cardiomyopathy and given this remains a clinical question, this patient population causes me some pause. We did have another patient who presented after discharge from another institution. They were placed on Hydroxychloroquine and they presented with long QT and cardiac arrest and unfortunately it comes secondary to neurological complications of their cardiac arrest. So, all these things caused me to wait for prospective data before I would make any recommendations in their use.

Thank you so much for those important key points. And with that, I think we'll have to close the question and answer session. But I really want to thank deeply appreciate our two presenters for their expertise in sharing their experiences with COVID-19 patients who are critically ill and pearls [phonetic] about clinical management. So really like to thank Dr. Michael Bundesmann and Dr.

Waleed Alhazzani. And then the slides will be posted on the CDC COCA webpages. With that, deep appreciation, I'll hand it back to Commander Khan. Thank you.

Thank you so much, Captain Uyeki. A closed caption video and transcript for this call will be posted on COCA'S webpage a few days after the live call at emergency. cdc. gov/coca. A video recording of this call will be available immediately after the call ends on COCA's Facebook page at www.facebook. com/CDCClinicianOutreachAndCommunicationActivity. Again, that web address is www.facebook. com/CDCClinicianOutreachAndCommunicationActivity.

Please continue to visit emergency.cdc.gov/coca over the next several days as we intend to host COCA calls to keep you informed of the latest guidance and updates on COVID-19. In addition to our webpage, COCA call announcements for upcoming COCA calls will also be sent via email. So please subscribe to coca@cdc.gov to receive these notifications.

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