[MUSIC PLAYING]

FARAAZ ALI SHAH, MD, MPH: So I will say that this was one of my dreams. When I actually first came to residency, I was in [INAUDIBLE]. [INAUDIBLE] this opportunity. Today, we're going to be going through 50 years of corticosteroids in sepsis, so get ready. This work-- I'll just mention-- I actually took the recent [INAUDIBLE] files, as well as a blood analysis through a word cloud, and that's what's generated this. I had to tinker with it a little bit because hydrocortisone and corticosteroids were a little too long for it. But apart from that, that's what generated this word cloud.

Before we get started too much, I do want to mention I do have a disclosure, if I move forward. So I am a co-investigator on a clinical trial that's looking at the effects of vitamin C, corticosteroids, and thiamine in sepsis. I did want to mention that. It's not a huge financial thing or anything like that, but I just wanted to mention that upfront.

So let's get started, and I promise this is the only slide that will have this much text on it. But I did think this was important because there's a lot of controversy about corticosteroids in sepsis, and I'll just read this out loud for everyone. So the role of adrenocorticoids in the management of infectious diseases has been the subject of much controversy. On the one hand, a large amount of information has accumulated to show that corticosteroids depress resistance to infection by reducing inflammation, inhibiting antibody formation, altering reticuloendothelial activity, and perhaps by other means yet to be discovered. On the other hand, corticosteroids have been shown, under appropriate conditions, to be anti-endotoxic and antipyretic and to influence vascular reactivity in a manner that might conceivably be beneficial to the infected individual.

This text right here is actually from the first trial of steroids in sepsis way back in 1963. And how far we've come. So let's go back-- let's go back to the beginning. I want you to picture the 1930s. Does anyone know where this is? This is the Mayo Clinic in Minnesota. I know-- and Minnesota is at the top.

[LAUGHTER]

But this is the Mayo Clinic in the 1930s. And this is where the miracle drug, corticosteroids, really get their birth. There were two individuals, Edward Kendall, who was a biochemist, and Philip Hench, who began work on isolating adrenal compounds in the 1930s. And the story goes that Dr. Hench, a rheumatologist, had a patient who came in with rheumatoid arthritis and she had an episode of jaundice and, afterwards, her arthritis spontaneously resolved. And through the years, he kept noting a number of other patients that would come in, some after surgery, some after pregnancy, and they would just have spontaneous resolution of their symptoms. So he was convinced that there was some compound in the human body that allowed this inflammation to resolve.

And with Edward Kendall, they started isolating compounds using adrenal glands from cows that were obtained from the local slaughterhouse. They were able to isolate six compounds which they labeled compounds a, b, c, d, e, and f. Compounds a and e seemed like the most promising ones to really mass produce because of the simplicity of their structure.

Well, they were doing this work in the 1930s. And then, late 1930s to 1940s, a considerable amount of funding went into trying to mass produce these compounds, and that event, of course, was World War II. Now, whether this was true or not, the rumor was that the German fighter pilots were using adrenal-derived compounds to-- they'd give it to their pilots and that would counter the effects of the altitude-induced hypoxia. That would make it so that their fighter pilots would be able to last longer in the air and make them better fighter pilots.

So a considerable amount of funding went into trying to use these adrenal compounds to maybe have a similar effect. Now, they didn't end up having the effect in the war that they'd imagined, but they were able to put this into clinical practice. And in the late 1940s, a young woman came into the Mayo Clinic with crippling rheumatoid arthritis. I believe she was in her 20s at the time. She received daily injections of compound e, which would later be found to be a corticosteroid, and she had resolution of her symptoms and walked out of the hospital three days later. The story goes that she went shopping afterwards, but that's beside the point.

But for this work-- and this was dramatic. For this work, they actually received the Nobel Prize just a few years later. So in 1948, they apply it clinically. Two years later, they're getting the Nobel Prize. And just to give a sense of these gentlemen and the work that they accomplished, Edward Kendall, before he was working on these adrenal compounds, actually isolated thyroxine. And the person in the middle, the Swiss biochemist, Tadeus Reichstein, he was working on the isolation of corticosteroids in a separate manner and received the Nobel Prize with them. But he'd done some work actually finding a process to manufacture vitamin C that was his own before he started working on adrenal compounds.

And Dr. [INAUDIBLE], we already talked about his work clinically. But the reason that a lot of these studies were delayed until the late 1940s was that, well, during the war, he was actually going to fight for the American cause. And then he came back and did his work that won him the Nobel Prize. So really the giants who came before us.

So 1948 is when we have our first clinical application of corticosteroids in sepsis. And then, in 1963, we have our first trial of corticosteroids in sepsis. And it's a pretty nice study. If you were to look at it under the standards that we have today, there'd be things that you would pick up that are different.

But this was a very ambitious study at the time. It was a multi-center, double-blind, placebo-controlled, randomized controlled trial. They were admitting patients that they had with a life-threatening infection, and they randomized them to receive a taper of hydrocortisone starting at 300 milligrams daily versus a placebo control. And they basically had-- they had vials that were [INAUDIBLE]. The patients didn't know, the physicians didn't know. And they gave 300 milligrams the first day, 250 milligrams the next day, 200 milligrams, and tapered off.

And the only outcome that they had was mortality. And they find here-- and you'll note, actually, that they group the patients into older and younger than 16 years of age. There was one site in their multi-center study that did enroll children. But looking at the adult patients, we actually see that in the cortisone group, you had a mortality of 56%. In the placebo group, you had a mortality of 43%. And this is-- so just think about that for a second. The first trial that we had of corticosteroids in sepsis was a negative study.

They [INAUDIBLE] number of different subgroups. They broke it out by age. They looked at-- and this is just one of the things that they looked at, the different types of bacteria that they had. If it was a pneumonia, they looked at different types of infection like meningitis. They looked at whether the patient-- excluding patients that would have died early on. But they really didn't find any difference. And actually, very astutely, they thought that when we do these small subgroup analyses, you should be very cautious because the numbers are quite small. So this is just for descriptive purposes, and not to make any assumptions.

So if we stopped over there, the bottom line would have been corticosteroids do not benefit in severe infections. But of course, we've kept going since then. And why is the reason for that? So why might corticosteroids in sepsis work?

Well, corticosteroids [INAUDIBLE] number of functions in the human body. There's a glucocorticoid receptor in almost every cell in your body. And the targets for glucocorticoids are quite vast. When we think about them in critical illness, we're typically thinking of them in terms of the stress response, or in terms of their effects on inflammation. As many of us know, there are signals, like from stress or inflammation, that signal the hypothalamus-- the pituitary gland-- to release ACTH, which [INAUDIBLE] from the adrenal glands.

We'll talk a little bit first about the effects on the immune system. And we know that there is a robust pro-inflammatory response in sepsis. It involves a coagulation cascade, it involves a number of different native new cells. And the early thought was, OK, so there's a robust pro-inflammatory response if you give corticosteroids in sepsis. And I put this up there like this for a reason. I don't want you guys to look through all of this, but this is just to demonstrate that there are a wide range of effects of corticosteroids on immune cells, repressing TLR4 signaling, effects on the endothelial cells, [INAUDIBLE], and influencing [INAUDIBLE] polarization. But it's not a precise instrument in information. It's kind of more of a blunt hammer.

And so we've had the first negative study, but then in 1976 is the first single-center study that really gets people trying to use corticosteroids in sepsis. And I would not recommend this to anyone just because the work involved-- I've seen from my own trial. This was a single individual at a single center over an eight-year period. Prospectively recruited 187 participants with septic shock, which he defined as someone with a septic history or some form of infection, a fall in blood pressure, and positive blood cultures.

He took those participants and he randomized them in what he describes as a blinded fashion to either receive dexamethasone, methylprednisolone, or a placebo and looked at an outcome of mortality. Now, for those of us that don't see corticosteroids that often, these doses are very high doses of corticosteroids. These are very, very high doses of corticosteroids.

He's one individual. He was recruited by himself. He paired this with another retrospective study of patients that-- about 328 participants who received varying doses of the corticosteroids, varying durations, and compared them to the patients that had not received corticosteroids and looked at their mortality. And his results were quite dramatic.

So when you look at the prospective and the retrospective study, in the group that did not receive corticosteroids, the mortality is around 40%. That's not too different from what you would've seen from corticosteroid trials at that time, if not higher. Sorry, of sepsis studies at that time. But that's an absolute risk reduction of about 25% to 30% because with corticosteroids, he was reporting that the mortality went down to about 10% to 15%. And if you think about that, with a treatment like this, [INAUDIBLE]. And so if you stopped over there, the bottom line was, high doses of short courses of corticosteroids will improve mortality in sepsis. But of course we know that subsequent trials just did not show that same benefit. And actually, they showed that there would be potential harm with corticosteroids. They showed that with these doses not only was there increased mortality early on, but there was also an increased risk of super infection afterwards.

And so let's take that off the board for a second and let's revisit the effects of corticosteroids on the immune system. So we know that we've got both our innate and adaptive immune responses, right? So if a patient is coming in with a large pro-inflammatory burst, the adaptive immune system is going to kick in. But as that adaptive immune system is kicking in, a lot of times we're putting corticosteroids on top of it.

And this, again, is-- I'll put a disclaimer out there. I know there's a lot of people who study corticosteroid biology and immunology, and I'll just say this is a simplification. But just know that there are effects of corticosteroids on T-cell maturation. You've got an active adaptive immune process going on, and you put corticosteroids on top and you're taking away from the TH1, TH17 response and particularly more to a TH2, TH regulatory response.

And it's not just a pro-inflammatory response. I think we're starting to understand more and more that at the same time as you had that large pro-inflammatory response in sepsis, you actually have a large anti-inflammatory response as well. And they had patients who settled in with some persistent inflammation, but you have patients who end up resisting immunosuppressed. It's very complex. And on top of that, if you're tossing out corticosteroids, we really don't understand the effects of these interventions 100% as yet.

So the enthusiasm for just taking down inflammation in sepsis, we've shifted away from that sort of thought, and a lot of what we focus on these days is thinking about what are the effects of giving these corticosteroids on the stress response? We know that the stress response is very important for a patient, like if you've got a patient that has immunoinsufficiency that are a lot higher risk to die of infection.

And there has been some evidence that there is a critical [INAUDIBLE] corticosteroid insufficiency. And there's a number of mechanisms that have been proposed for this, including cytokine-induced glucocorticoid receptor insensitivity. And there have been studies that have shown that when you have relative corticosteroid insufficiency, it's associated with worse outcomes.

This is data from one study. It was a very small study looking at about, I think, 150 patients that were admitted with abdominal sepsis. And in this study, they found that the level that they saw that would discriminate survivors and non-survivors was that the non-survivors seemed like they had-- and I'll see if I can pull it up right here. It seemed like the non-survivors were the ones that weren't able to, in response to a [INAUDIBLE] stem test, were not able to amount an adequate cortisol supply. I'm going to talk about that in a bit, but just know that it may not be the absolute cortisol level that you have, but it seems like being able to have a response to cortisol is a negative prognostic sign in critically ill patients with sepsis.

But this, I'll just say-- before I get into too much about cortisol levels and cort stem tests, I'm just going to say upfront that determining adrenal insufficiency in critically ill patients is tough. In a non-critically ill population, if you had a random cortisol level that was less than 3, that would be diagnostic. In a patient that is not critically ill, and you have a random level that was greater than 12, you could pretty much say this person is not adrenally insufficient. But these thresholds are not well characterized in critically-ill patients.

And before we even get to the critically-ill patients, I'm also going to mention that this is what your cortisol looks like throughout the course of the day. There's a circadian rhythm to you cortisol, but there's also an ultradian rhythm as well. There's oscillations within the circadian rhythm. And you can see that-- this is from a healthy volunteer that was having their cortisol checked every 15 to 20 minutes.

You can see that even around that time of that 8:00 AM cortisol, where we sometimes try to check it in our patients that are in the hospital, there's a pretty wide variation. If you had the level checked maybe 15, 30 minutes earlier, you'd get quite a different result than 15 to 30 minutes later. And this is a patient that's healthy, not in the hospital, doesn't have their circadian cues all thrown off by a critical illness by the lights being on and off at different times. So this is just to add on that it's going to be difficult to determine your cortisol responses and your-- just really assessing where you are in your circadian rhythm in critically-ill patients.

AUDIENCE: [INAUDIBLE]

FARAAZ ALI SHAH, MD, MPH: Yes, it is.

AUDIENCE: [INAUDIBLE]

FARAAZ ALI SHAH, MD, MPH: Yeah. So in a number of these studies, they've looked at-- and they have looked at patients that were responders versus non-responders. And in a number of these trials-- not a number of them, but in several of them, they did try to determine where the patient was in their-- whether they were premenopausal or postmenopausal, and which stage of the menstrual cycle they were in. Because you're right, that does have an effect in having [INAUDIBLE]. But again, those were smaller numbers because they were broken into groups.

Also, just another thing to mention about measuring cortisol responses. So remember that free cortisol is a very, very expensive test. Most of the times what we're getting is the total cortisol. And that total cortisol is going to be-- the free cortisol is really going to influence whether you're going to have a robust response or not. And there's a number of cases in which you may have your cortisol body logged and it's quite high, like if someone's on OCPs or if you've got hyper [INAUDIBLE]. And you may get a false negative in those settings.

And you may get a false positive from patients where that CBG is low, and that can happen in patients with nephrotic syndrome, with cirrhosis, and very important for outpatients, in malnutrition as well. So I mentioned this and I'm not going to go too much further into it, but just to let you know that when we do talk about these patients, a responder versus a non-responder, we're using cut-offs that it's not that easy to determine who is a responder and who's not.

But that does lead us to our next trial. This is the next really big trial that helps influence how patients receive steroids in sepsis. And this was a [INAUDIBLE] study that was done in 2002. I was going to make the point that this was a great year in critical care, 2001 to 2002, because you had so many studies that were coming out that showed that we can improve mortality. You had tight glycemic control, reduces mortality, activated protein C, reduces mortality. Rivers protocol, reduces mortality. And here, the United study, reduces mortality.

So what they did in this study-- it was a study where they recruited 300 mechanically ventilated patients in septic shock from 1995 to 1999. And just remember that I mentioned that a lot of those studies came out at the same time. So know that the standard of care was different. You didn't have the [INAUDIBLE] trial come out just yet.

And these patients received hydrocortisone, 50 milligrams every six hours [INAUDIBLE] cortisone, 50 micrograms daily versus a placebo. So just taking a step back, these are natural and synthetic occurring corticosteroids. [INAUDIBLE] corticosteroid, but there is a difference between corticoids and [INAUDIBLE] corticoids. We see that hydrocortisone is one of the medications that we use pretty frequently in the ICU, and it has pretty similar levels of activity on glucocorticoid and mineralocorticoid receptors. Glucocortisone has predominantly a mineralocorticoid effect. Prednisone and methylprednisolone have more predominant glucocorticoid effects, and dexamethazone is thought to be primarily glucocorticoid-receptor active.

So in this study, they're getting both hydrocortisone and fludrocortisone. The hydrocortisone dose that they give, they're giving about 200 milligrams of that cortisone. They're getting about 160 of mineralocorticoid activity. And if you're getting fludrocortisone and you're giving a 15-microgram dose, on top of it, you're really getting somewhere about 5 to 10 extra. But just keep that in mind moving forward as we talk a little more about these studies.

So they did do-- they did a-- and I know a lot of us know this study, but I did want to go through it because we're going through 50 years of corticosteroids in sepsis and this was one of the great turning points. So they did a high-dose ACT stem test and they declined people who were non-responders. If they did not-- regardless of what their baseline cortisol was, if they did not get a response that was greater than 8, they considered that patient to be a non-responder. And recruited 300 mechanically ventilated patients. They didn't know what the results of the stem test were, but they empowered themselves to detect a difference in the non-responders. So they assumed that there would be a higher proportion of patients that were non-responders.

And in this study, the primary thing that they found-- there's a couple things. So in the study, the mortality in the group of non-responders without any treatment was 60%, and these were septic shock patients. So this is quite a high mortality. And I think nowadays, if we saw that type of mortality in a clinical trial, we would be very-- even in a group of patients with septic shock, we would say this is too high. Something seems wrong with this study. And in the non-responders, it was around 50%.

Now, when these non-responders received corticosteroids, they had a 10% absolute risk reduction, which is a very profound risk reduction. And this p-value over here that they're showing about the mortality, well, the p-value is significant, but that p-value actually comes off of a statistic regression model. And when you actually look at the unadjusted difference in mortality, that p-value goes to 0.11.

This is a small study. I'm not saying there's not a difference there, but I'm just saying that what was put out as saying there's a statistically significant difference, we just want to keep that in mind. There are some other things to note about the study. As you'll see with many of the other studies that have come, we did note that there was a decrease in-- sorry, I should say that in the patients that received corticosteroids, they were able to come off the base repressors earlier.

But one other note about this study, when we think about it in the terms of the patients that we have today, is that the mean time to get appropriate antibiotics in this study, which they described as prompt being less than 24 hours, that was actually about six hours. So it's very different from the care that we're providing right now. But if we stop right there-- oh, did anyone have a question?

AUDIENCE: Is it [INAUDIBLE]?

FARAAZ ALI SHAH, MD, MPH: Yes, it is.

[LAUGHTER]

Ian will tell us about that a little bit later.

[LAUGHTER]

AUDIENCE: It can show us the mortality. It shows the survival [INAUDIBLE]. There's a big difference. That's a big problem with all these studies.

FARAAZ ALI SHAH, MD, MPH: Correct. Correct.

AUDIENCE: So how did you know on the next slide?

FARAAZ ALI SHAH, MD, MPH: Is it? Well, it is, but that's right.

[LAUGHTER]

We're going to get there.

AUDIENCE: Why should we be doing chest x-rays for lung cancer screening?

FARAAZ ALI SHAH, MD, MPH: Well, I'll get to that. I'll get to that, get into that. And of course, a lot of us know these studies, but the next big study that looked at this was, if we stop right here, that's what some of us would be thinking. But this did really raise enthusiasm for the use of corticosteroids in sepsis.

A follow-up study that enrolled about 500 participants came just a few years later. And this was a time when-- I mentioned a lot of those studies. 2008 comes around, right? Young Matt [INAUDIBLE] is just coming out of fellowship and my sugar comes out and says, you know, your intensive insulin treatment maybe doesn't have that mortality benefit. You get [INAUDIBLE] coming out, which is saying, you know, your activated protein C, maybe there isn't that same mortality benefit.

And according to a study which randomized participants to receive hydrocortisone versus a placebo, and was actually powered to try to go into about 100 patients, but enthusiasm for the trial had waned and they could only recruit 500. It didn't really show any difference in your mortality. It doesn't matter where you look along the time for this-- your survival or your mortality. But it doesn't matter where you're looking along this whole 28 days. You really didn't see a benefit anywhere.

There did seem to be a benefit when you looked at all patients, in terms of coming off of a vasopressor earlier. I used the term shock reversal, but I'll just-- I'll admit that it's not really true shock reversal. It's coming off of [INAUDIBLE] defines inadequate delivery of oxygen to your tissue. But what they're talking about is coming off the vasopressor. And actually, that effect seemed like it was more or less in patients that still had their response from stem tests.

So very quickly, we're taking this off over here. Low doses and long courses of corticosteroids don't reduce mortality in sepsis. So where does that leave us? Well, the Surviving Sepsis guidelines that come out after this study just say, consider corticosteroids in refractory vasopressor [INAUDIBLE] shock.

AUDIENCE: [INAUDIBLE] One of the differences also [INAUDIBLE] is the level of [INAUDIBLE] in the groups.

FARAAZ ALI SHAH, MD, MPH: And I didn't go through it as much as-- I think I might have in an earlier talk. But there are quite a few differences in that sense. So first off, they didn't use the cortisone. Second off, the duration of steroids that they used in this trial was a lot longer. They basically had seven days upfront. They were using hydrocortisone-50 for 50 milligrams every six hours, and then they tapered it off over the next five days. Or it was like six and then five.

And similarly, their window of enrolling patients into CORTICUS was actually 72 hours, so a much longer window to try to enroll someone. Those are important differences. So there were a number of studies that after CORTICUS that just-- again, they did not demonstrate a benefit from corticosteroids in sepsis. We had the [INAUDIBLE] study, which I'll actually come back to in a bit, which was the two-by-two study looking at norepinephrine versus vasopressin in patients with septic shock, and also looked at hydrocortisone versus placebo.

You had the [INAUDIBLE] study coming out of Germany, which tried to take patients that had septic shock and tried to see if randomizing them with hydrocortisone versus placebo could prevent them from coming onto vasopressin. But that, again, did not show a benefit for corticosteroids in those patients with severe sepsis.

But it's 2016 to 2018, we are revisiting this again because of the publication of some very-- two very nicely done randomized control trials, and one other study that I'll discuss. And so let's talk about these trials, the ADRENAL trials, the APROCCHSS trials, and the study of vitamin C along with thiamine and corticosteroids in sepsis. This has been in the *New England Journal.* It's been in the news. It's been on Facebook.

[LAUGHTER]

Let's talk about-- it's 50 years. How far we've come. So let's look at the ADRENAL study and the APROCCHSS studies. So these were two very, very-- these were probably the two largest randomized control trials that we've had looking at this question of corticosteroids in patients with sepsis. And ADRENAL randomized patients to receive a hydrocortisone infusion for seven days versus a placebo control. And APROCCHSS used the study that was done-- used the same formulation that was used in the 2002 study of hydrocortisone versus fludrocortisone. I mean, fludrocortisone versus a placebo. It was not compared to hydrocortisone, and I'll come back to that in just a moment.

ADRENAL recruited 3,800 participants from 2013 to 2017. This was the ANZICS group that comes out of Australia and New Zealand, and so it was a multi-center study in Australia, in the UK, New Zealand, Saudi Arabia, and Denmark. And the APROCCHSS study, in contrast, did recruit a smaller number of participants. They recruited just over 1,200 participants over 2008 to 2015 in 3,400 ICUs.

Both of them were trying to enroll patients with septic shock within the first 24 hours, and both of them had a primary outcome of all-cause mortality at 90 days. The inclusion criteria differed a little bit. For the ADRENAL trial, you had to have a clinically documented or highly suspected infection, and you had to fulfill at least two or more of the criteria for the systemic inflammatory response. That was how we were thinking about defining sepsis at the time these statements were initiated. It's not exactly how we define it these days. And you had to be on vasopressin therapy for at least four hours prior to randomization.

So for the APROCCHSS study, you had to have the same sort of clinically and microbially documented infection, but you needed to have a SOFA score of 3 or 4 for at least two organs for at least six hours' duration, as well as vasopressin therapy for at least six hours to maintain your systolic blood pressure. This is a lot stricter criteria than what you're going to have for ADRENAL.

And in terms of the exclusion criteria, as well, it does create some differences because in the exclusion criteria for ADRENAL and APROCCHSS both exclude patients that have gotten corticosteroids and have septic shock that's been greater than 24 hours. But for patients in the ADRENAL trial, they excluded patients that had received [INAUDIBLE] because it has effects on your cortisol axis. And they also excluded patients that they thought might have a bad 90-day prognosis. They didn't define that strictly, but it was just kind of additional.

The APROCCHSS trial, in contrast--

[LAUGHTER]

No, no. I think it was apart from sepsis, I should say. But the APROCCHSS trial excluded patients with a high risk of bleeding, and I'll talk about that for a second. Some of you might already know what the reason for that is. And they also excluded patients that were pregnant. I actually think that was an exclusion criteria in ADRENAL, as well, so I forgot to put that up there.

You can see that the mortality in the control arms of both of these groups was very different. So for the ADRENAL trial, the mortality was close to 30%. For the APROCCHSS trial, your mortality in the untreated group was close to 50%. So this seems, overall, like a sicker cohort of patients.

Now, ADRENAL was powered to detect a 5% absolute risk reduction with 1,900 participants in each arm. That would give you about 90% power to detect that data. APROCCHSS was powered with 90% to detect a 10% absolute risk reduction with 320 participants in each arm. And the reason that they actually doubled that amount is because when they started the trial, it was actually a two-by-two trial that was going to be studying activated protein C versus placebo and hydrocortisone versus placebo. Hence the exclusion criteria of a high-risk of bleeding.

But when the trial got underway, they took activated protein C from the market and they just went forward and just kept enrolling participants. But keep that in mind that it was powered initially to detect a 10% absolute risk.

AUDIENCE: [INAUDIBLE]

FARAAZ ALI SHAH, MD, MPH: Yes, yes, they do.

AUDIENCE: [INAUDIBLE]

FARAAZ ALI SHAH, MD, MPH: Yes.

AUDIENCE: [INAUDIBLE]

FARAAZ ALI SHAH, MD, MPH: And they do get-- I know they have a data that's more granular. They haven't published everything, but they do have data that's more granular. And you get some sense of it from what they do give you. So in terms of age and how many male-- what proportion were male participants, the ADRENAL and the APROCCHSS trials are fairly similar. But the Approx trial tended to admit patients that came more to a medical ICU. ADRENAL had a greater proportion of patients that came from a surgical ICU, in comparison.

And Approx did have patients that were more pneumonia sepsis. The rates of renal replacement therapy were also higher in the Approx trial, as well, going along with a higher burden of disease. And they do break down in the study-- I don't have everything here-- but they do break down, in some of their appendices, what type of organisms were seen more commonly.

So that's how the trials are similar and different before we get to the results. And when we actually look at the results, well, in the ADRENAL study, which again, was looking at a hydrocortisone infusion versus a placebo control, they didn't see a difference. This is consistent with what we've seen in a lot of previous studies of corticosteroids in sepsis. It's consistent with the CORTICUS trial. It doesn't matter really where you're looking, you can see a difference between these two groups.

And they did break it down in a number of pre-specified sub-groups. And they didn't really find anything that looked like a very compelling subgroup of patients that would benefit. But of course, these trials came out at the same time. And I'm trying to remember-- someone can correct me. I'm pretty sure they came out in the same issue of the *New England Journal of Medicine.*

The one thing I will say about ADRENAL trial is consistent with, again, a lot of the earlier studies, they did say that the time to come off of the vasopressors was earlier if you were in the hydrocortisone group. And this was a pragmatic trial, so a lot of the adverse events were just kind of if the site investigator felt it was important enough to report. And adverse events that are listed are fairly low. And there isn't too much that seems like it's overwhelmingly convincing that this is an adverse event that you get a lot more with hydrocortisone.

When we look at the Approx trial, they looked at fludrocortisone. And the ADRENAL did not look at fludrocortisone because they say we did not administer it because it has previously been shown to be ineffective. And where does that study come from? It's actually another earlier trial that was looking at-- in, again, a two-by-two design. It was looking at intensive insulin therapy versus conventional glucose control and hydrocortisone versus fludrocortisone. All the patients in this trial got hydrocortisone, every one of them. But it was just a question of maybe it's because of differences in hyperglycemia. You get those under control, the mortality is different. That was not the case.

And when they looked in this study, where they had about 500 participants in each arm looking at the effects of hydrocortisone versus hydrocortisone and fludrocortisone, they did not see a difference in the mortality rate. But then they took it from 500 patients 1,240-something patients. And here, they did see an improvement in survival.

So when you look at the much larger study here which, again, was initially designed to detect an absolute risk difference of 10% in half as many participants, you do see an absolute risk reduction of 6% in the study at 90 days. Now, the p-value [INAUDIBLE] by the law of rank test, if you just stopped it at 30 days, it doesn't actually end up being quite as strong. It's really when you're taking it up to 90 days that they see this difference in survival.

AUDIENCE: But, Faraaz, the former study has the similarity [INAUDIBLE] because it has that [INAUDIBLE] 95.

FARAAZ ALI SHAH, MD, MPH: Yes, you're absolutely right. You're right. But it's going to come into play, I think, a little bit when we talk about what the effects of corticosteroids in sepsis are. Because I agree with you that compared to the previous trial, you're right, that is within what you would have expected to see. But I think when you think about if someone were to do another study of corticosteroids in sepsis, just thinking about what's the magnitude and the difference you're going to see-- and I'll get to that in a little.

AUDIENCE: Because your [INAUDIBLE] will not show that there is a heterogeneous effect within the sub-group. So is it just because of the super heterogeneity of the former study and little heterogeneity in this study?

FARAAZ ALI SHAH, MD, MPH: That is a question that really should be studied a little further.

[LAUGHTER]

AUDIENCE: There was a big difference in the norepinephrine dose of those two studies. The patients in the APROCCHSS study were sicker.

FARAAZ ALI SHAH, MD, MPH: Yes.

AUDIENCE: If you think about the enrollment criteria, they enrolled patients in septic shock with multiple organ failure. The other study enrolled patients on some vasopressors who had SERS criteria, which most of our ICU patients have. And there was a significant difference in the norepinephrine dose that these patients were on.

FARAAZ ALI SHAH, MD, MPH: Yes, that is correct.

AUDIENCE: Just thinking clinically about who were the patients that we see that either [INAUDIBLE].

FARAAZ ALI SHAH, MD, MPH: Great.

AUDIENCE: Can you go back to the overall mortality from the INTRIGUE studies [INAUDIBLE] 5%? Right, right, yeah. So 55% survival versus 75% survival [INAUDIBLE]. OK.

FARAAZ ALI SHAH, MD, MPH: Correct. And again, and I did show this data from ADRENAL as well. It was consistent in getting patients-- giving a combination of hydrocortisone and fludrocortisone. It did seem like it got patients off the vasopressors earlier and got them off mechanical ventilation earlier as well. And that was something that actually was shown in the ADRENAL trial as well. So those findings are consistent.

When you look at the adverse events here, there's a number of adverse events you think about with corticosteroids. The big difference that they saw in this study was the difference in hyperglycemia, where it was higher in the group that got treated with corticosteroids. Some of the other things that we get concerned about, GI bleeding, did not differ significantly between the groups. And they report that they did not see any difference in super infection in their study when looking out to 90 days.

There are some longer-term studies that are going to be coming from this trial as well. I actually forgot to check to see if it was published recently, but there is some one-year data that's coming from the ADRENAL study. And I think there's some that's planned for this study as well.

But where does that take us right now? Some might look at this study and say, well, it looks like hydrocortisone alone doesn't work, but maybe if you combine it with something, that's what we need to really get things working. And I'm going to go ahead and say I don't think that's the case. I really don't.

And that's especially important when we think about the metabolic resuscitation in sepsis because this is a very hot topic. A lot of people who I'm trying to enroll in my study in the ICU are asking me, well, why can't you just give them the vitamin C and thiamine in that one? And I'm saying, well, here's the reason.

[LAUGHTER]

So what have they done in this study? This has become very much in the news because the lead author of this study took patients who-- the story he gives is that he had a woman who was going to die for sure in front of him with septic shock. He had nothing left to offer her and he gave her a cocktail that was derived from his understanding of what happens to patients in sepsis. And he gave her a combination of vitamin C, thiamine, and stress-dosed steroids. And the term he describes is that organ failure just melted away. That patient who would have died just miraculously was off of the vent and going home. And he tried this in two more patients, and then he just started giving it to every one of his patients upfront.

And what he did was he took 47 patients that he gave this protocol to and compared it to 47 patients before he really had this protocol going in his institution. And he did a propensity-based analysis where he incorporated number of variables that you might think would impact the mortality, and just did a before and after study.

And the results that he reports do seem pretty dramatic. When you look at what the mortality went to, the 47 patients that they looked at before had a mortality that was around 47%-- around 40%, I should say. And then with the protocol, these patients dropped down to a mentality of about 10%. And again, when they looked at the SOFA scores in sequential days, it was the same sort of-- it just seems like things are melting away.

But this isn't-- I would just say there are trials-- and again, I mentioned I'm part of one of the trials that's looking at this-- that will test this way that we should test any interventions. But just know that this isn't in use. I don't think that this would be strong enough for me to go up to my patient and say, if I'm not giving this to the patient, I'm giving them some harm. I'm not saying that there isn't any benefit here, but I would say that I'm definitely not convinced by just this study alone. But it is something that-- there are, I think, about four or five trials that are looking at this ongoing that should be published in the coming years.

So I think where we are right now is still where I think the bottom line is at this moment. I'd still say you can consider a patient that's got refractory-based vasopressor-dependent shock. But where are we headed? Well, before we think about where we're headed, I'd like us to just think about where are we right now? Well, first of all, do we need another large randomized control trial? Do we need another really big one?

And there's some things that I'll just say upfront. So when you look at how many trials have been done on corticosteroids in sepsis, you've had over 42 trials that-- and these are the 42 trials that they've included in this-- this was a clinical practice guideline. And they've enrolled over 10,000 patients with sepsis into trials of corticosteroids. And I don't think we've done that really for many other things in sepsis. And it's, I think, one of the unique sort of treatments that we just kept trying to test over and over and over again. Maybe wet versus dry would be another one.

But when you look at these studies, most of them have looked at hydrocortisone alone. Most of them have looked at a longer course and a lower dose, and most of them have been looking at patients with septic shock. And when you look at the 35 studies that have looked at this low dose, longer course, when we look at the overall mortality, you can see the mortality does vary quite a bit trial to trial.

And when they did-- this was from a meta analysis that was done recently. They found an absolute risk reduction when you're looking at 28-day mortality or you're looking at mortality-- they put a time frame of 90 days to one year. You're looking at an absolute risk reduction of like 2%. So if you're thinking about doing the next study of corticosteroids in sepsis, just keep that sort of a number in mind because it's not like it's not important. Like, to treat 50 is still something that we consider doing in our clinical practice. But if you're trying to do a clinical trial, you're going to need a whole lot of patients to really show a difference that's going to be this 2% absolute risk reduction.

And there is heterogeneity in these trials. They do say that-- one thing that's come out is-- some of the things that they said could be beneficial even apart from the mortality would be an increase in shock reversal, reduced time in the ICU and in the hospital. But let's take a little bit more of a look at that.

So for shock reversal, I'd say the data seems like it's all going in the same direction. It seems like patients come off the vasopressors earlier when you give them corticosteroids. But in terms of your ICU length of stay and your hospital length of stay, I would just say you don't see that same sort of slam dunk. This is going to help patients get out of the ICU, get out of the hospital. That can be still something that's clinically relevant.

And in terms of the side effects, in this meta analysis, they found higher rates of hyperglycemia and hypernatremia. That's not too-- that's nothing that's too difficult to manage. But a number of the other things that you might think about, like long-term neuromuscular weakness, they just haven't been able to really study, or long-term cognitive issues as well. And they make a point in here that there's more benefit in any substance that they looked at in this meta analysis. But it could be they would take a different type of approach.

Now, I know that some of the people in the room are actually doing this even better than I've been attempting to, but there's this big focus on trying to really look into-- the same way in cancer therapy, we've been able to tailor the right therapy to the right patient. There's an approach we're trying to take, trying to find how septic patients are different. And this was one approach that took a neural network approach from the Intermountain group. And they looked at all their patients and just tried to assign them to different clusters.

Each one of these numbers over here represents a different group of clusters that seem like they behave similarly. Group 1 over here is a group of patients that predominantly have more substance with multi-organ dysfunction as defined by renal failure. Group 2 has it spread mildly across a number of different organ systems. Group 3 tends to have more of a pneumococcal, more of a pneumonia, hypoxia-type dysfunction. And Group 4 tends to have more liver dysfunction.

When you look at the survival within each of these different clusters, it's different. Groups 1 and 2 have survival that's better than 3 and 4. And if you were to build logistic regression models that predicted survival, there's different variables that go along with cluster 1 and 2 than would go along with groups 3 and 4. For example, lactase is very predictive in, say, for example, Group 3. And it just really isn't as much in Group 4, for example.

AUDIENCE: [INAUDIBLE]

FARAAZ ALI SHAH, MD, MPH: Yes.

AUDIENCE: [INAUDIBLE]

FARAAZ ALI SHAH, MD, MPH: Yes.

AUDIENCE: [INAUDIBLE]

FARAAZ ALI SHAH, MD, MPH: I can answer that in saying that they really, in that study, they said that there really weren't very many side effects with vitamin C. The trials that we're doing right now will be looking at a number of different ones. I think one of the things that you get concerned about is the risk of renal failure when you're getting high doses of vitamin C like that. In terms of these precision medicine approaches, are they incorporating things looking at antioxidant levels? I think they're at a very early stage with that. They're still at the stage where they're trying to incorporate biomarkers, proteomics, genomics. I think we're at the very early stages of that, so it hasn't been done quite yet. But this was just to illustrate that patients with sepsis may not all be one group.

Well, let's think about precision medicine approaches and then see if we can use this to try to find the patients that are benefiting with corticosteroids. So this was one study that was [INAUDIBLE] Intensive Care Medicine where they did secondary analysis of patients that were enrolled in a trial that looked primarily at norepinephrine versus vasopressin.

So a number of these patients got corticosteroids and, for the most part, they were getting hydrocortisone doses that lasted about seven days. They used a propensity score matching approach to find patients that had received corticosteroids in the past, and then they formed baseline cytokines on all them before they had gotten corticosteroids, at least for the core group of patients that they did have blood that they could do that on.

And they looked at individual cytokines. And if I remember correctly, I think CD40-lygin was one that, when you looked individually, it had had the best ability to discriminate between patients who would and would not respond to steroids. But it seemed like when you took triplets of cytokines, that had the best predictive ability. And a combination of IL3, IL6, and CCL4 had the highest predictive value in response to steroids.

So in this trial-- again, what was not really looking at steroids versus not-- they did find that in a propensity-based analysis, the red lines represent patients who were above this threshold. So their cytokines were above this threshold they needed for IL3, IL6, and CCL4. When you were above that threshold and you didn't get steroids, you had actually what looked like a worse survival than if you actually received steroids.

But if you were below that threshold, it actually seemed like it was reversed. So patients with these high levels of cytokines, in these three cytokines in triplet, may have a benefit if they get corticosteroids. But if they're below that threshold, maybe you're not actually benefiting them. Maybe you're even harming them potentially.

And they did often do this in-- in this cohort of patients, they didn't do a confirmatory analysis as yet in another study. But again, I know what you're saying. You guys are saying this is not a trial of corticosteroids in sepsis. You can't just apply it. OK, I agree with you.

So before I get to that, though, let me just take another approach that's common to try and define phenotypes in sepsis. So this was one that came out of Julian Knight's group in the UK, and they have a cohort of patients that have pneumonia sepsis. And they did transfer and analysis of peripheral blood leukocytes in patients that were admitted with sepsis and community-acquired pneumonia. They had a discovery cohort of about 265 participants and a validation cohort of about 106. And they used an alumina chip to try to get different-- to look at the RNA transfertomics.

And their key findings-- I'm really summarizing down. It was a great paper. If you guys haven't read it, you have to take a look at it. Really what they found was they either grouped things into two key-- rather I should say they conclude the transfertomic signatures into two key [INAUDIBLE].

One that seemed like it was a quote, unquote "immunosuppressed" and maybe endotoxin tolerant phenotype, which is SRS1. And an immunocompetent one, SRS2. And when you looked at things that differentiated it, SRS2 had-- it would go a lot more with T-cell activation. SRS1 would go along more with something like apoptosis and cell death, things along those lines.

When they looked at these SRS1 and 2 phenotypes-- SRS stands for sepsis response signature-- it looked like immunocompetent SRS2 phenotype has a higher-- oh, it came out kind of blurry-- it had a higher survival in both the discovery and the validation cohort compared to SRS2 immunosuppressant phenotype. So well, we've got these nice phenotypes, but do they respond differently to different treatments?

AUDIENCE: Hey, Faraaz.

FARAAZ ALI SHAH, MD, MPH: Yes.

AUDIENCE: What was the split on the populations? How many-- what was the constituency-- [INAUDIBLE]?

FARAAZ ALI SHAH, MD, MPH: No, it was about, I think, 60/40.

AUDIENCE: OK.

FARAAZ ALI SHAH, MD, MPH: About 60/40.

AUDIENCE: For SRS2?

FARAAZ ALI SHAH, MD, MPH: In this one, I think it was more SRS2, yeah. The numbers are right here.

AUDIENCE: [INAUDIBLE] right there.

FARAAZ ALI SHAH, MD, MPH: They're small numbers, by the way.

AUDIENCE: That's OK.

FARAAZ ALI SHAH, MD, MPH: It's still expensive.

AUDIENCE: Faraaz, I just had a question on how the samples were prepared. Was there any filtering the immune cells to ensure homogeneity in the population for the [INAUDIBLE] analysis [INAUDIBLE] another possible explanation for the difference in signals and differential composition for a heterogeneous population?

FARAAZ ALI SHAH, MD, MPH: They did. To be honest with you, I don't understand the specifics of it so much. I know they did use specific tubes for collecting the leukocytes, and they used a B column to try to separate out the leukocytes that they were interested in. But the exact details of that, I'm not 100% sure.

AUDIENCE: All right.

FARAAZ ALI SHAH, MD, MPH: OK, so we've gotten these things. Well, what happens when you take it to a trial that actually looked at the differences between steroids versus placebo? This is a post hoc analysis of one of the studies that I mentioned earlier that was looking at norepinephrine versus vasopressin and hydrocortisone versus placebo.

So in this analysis, you see that they were able to perform their transcriptional analysis on 176 participants. And that was about split close to half of that between SRS1 and 2. And again, I know that the numbers are small. But when they look at differences in SRS1 and SRS2, it didn't really matter if they got norepinephrine or vasopressin. There was no interaction between your sepsis response signature and survival when you're including an interaction with the type of vasopressor.

But when you apply it to use of corticosteroids, you actually get something interesting. So here, this SRS1 phenotype is the one that was immunosuppressed. Hydrocortisone placebo, it seems like your survival was fairly similar.

And this-- again, I'll just remind everyone-- this was a trial that was negative, in terms of they did not show any benefit with corticosteroids in sepsis. When you look at just the patients that had that SRS2 phenotype, it actually seems like the survival is worse if you give that-- sorry, this is the immunocompetent one. It actually looks like there might be harm in the immunocompetent group. And I think that's important because most of what I've shown you so far has just been saying steroids may not have a great mortality benefit, but it seems like it gets patients off depressors earlier, it gets people off mechanical ventilation. It doesn't seem like there's any harm except for a little hyperglycemia.

And I think as we start to fine tune how we define sepsis, and as we start to fine tune which patients may or may not benefit to a treatment, we may end up finding patients that actually do get harm from the treatments that we think may not really have a-- that may not have an adverse effect.

So I think that takes us to what my bottom line is. So the bottom line that I'll say is that we still have some work to do. It's easy to look at these trials and feel like I don't think we know what we're doing with sepsis. I don't know if we should ever use steroids in sepsis. But I think it just-- I think it just shows to us that there's a lot that we can learn. And I think there's a lot of opportunity to keep trying to do work that'll improve patient outcomes. All right, that's it. Well, thank you guys so much.

[APPLAUSE]