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TRANSCRIPT - GR 08 26 22 ***"Hepatoacrenal Syndrome"*** – Brian Wentworth, MD and Helmy Siragy, MD from the University of Virginia

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Addison Hicks

00:20:38Well, thanks for coming out to Medicine grand rounds everyone today. We will be extra special. We need to hear from two Uba physicians, Dr. Helmy Siragy and Dr. Brian Wentworth. Dr. Siragy is a professor in the Department of End Technology, and holds the Harrison distinguished chair of Excellence in medical education.

Uthlaut

00:20:55Uh, he obtained his Residency training in Texas, uh Galveston, and then fellowship's endocrinology and hypertension at Texas as well in San Antonio is a Fellow of the American College of Physicians in the American Heart Association,

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00:21:09and as a member of numerous national and International Endocrine and Hypertension Societies.

- 00:21:16An international lecture on subjects related to hypertension and endocrinology. Dr. Siragy i was the first to discover and publish the stimulation of Andrea Tensin, a two hundred and twenty two receptors leading to the generation of nitric oxide media. Through Brady Tiden,
- 00:21:32Dr. Siragy has authored more than one hundred and fifty medical journal articles and twenty one medical textbook chapters, including the chapter on Kidney and the Ren and Andiotensin System in the Runwall at Atlas of Heart disease
- 00:21:46and Angiotensin and Diabetic nephropathy In Harrison's online textbooks of medicine.
- 00:21:52Dr. Sarahi is joined today by Dr. Brian Wentworth.
- 00:21:56Dr. Wentworth is an assistant professor in the department of the intro of gastroenterology and hepatology.
- 00:22:04Oh, and they just started moving their sides. Interesting!
- 00:22:07He completed his medical school training at Rutgers University, followed by his Internal Medicine Residency here at Uva, and subsequently a fellowship,
- 00:22:19gastroenterology, and hepatitology. He,

- 00:22:24you know, I think he's been quite a research mentor to a lot of the young residents that are kind of going up to the ranks here, looking at A. Cv. We have names from many past residents and current residents on some of the app on the abstracts and posters that are on a Cd. Which is really a dedication to his attempt to try and give back what he's. Um! What he's developed over the years.
- 00:22:46Um,
- 00:22:48So what I thought was impressive, too, is on top of completing a fellowship. He did an advanced fellowship in hepatology,
- 00:22:55a transplant, and then a masters of science and clinical research. Just before joining our faculty in two thousand and twenty one. His research focus is defining the path of physiology and a prognosis of adrenal insufficiency and cirrhosis. That will be what today's talk will be about. We have two wonderful speakers. So please give a warm welcome to Dr. Siragy and Dr. Brian levy
- 00:23:23it
- 00:23:25to make sure
- 00:23:27that's all. I'm working

Unknown Speaker

00:23:29It's working. Okay,

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00:23:31he'll be fine.

- 00:23:34Well, thank you, Sam, for that very kind introduction, and it's wonderful to be speaking here. Um! A lot of familiar faces, and some that aren't. But um, you know Helm and I are pleased to talk about this, and I think this has become a topic that obviously is of great interest to both ourselves. For a research perspective. I think I’m starting to talk about this more and think about this more, and I know a lot of our residents have come interested this topic as well.
- 00:24:01So these are just our disclosures. So basically, just relate to research funding we both have.
- 00:24:07And before I start I just want to sort of say, you know as same point out. I've been here now eight years, and it's been a wonderful place for my wife and I and our daughter to grow up and mature.
- 00:24:18And um! I had a wonderful time here, Residency, and made lots of friends, and these are some pictures from uh past years here. Um! And I think one of the best things we could do here is our sense of teamwork and collaboration really has made this possible, and some of the mentors I've had to help uh start me on this pathway and instrumental. So I want to say Thank you. And I hope you guys all kind of take advantage of the opportunities here.
- 00:24:41So to sort of talk.
- 00:24:43Talk about this right? We're talking about adrenaline's efficiency in cirrhosis,

Brandy

00:24:47And I think the old way to think about This is this is a topic that kind of bridges, the disciplines of hepatology and endocrinology.

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00:24:55But like a lot of medicine, especially these days, I think it's more important to think about this in a new type of paradigm framework.

- 00:25:05I think it's really important that this
- 00:25:08is a topic that bridges both our intensivist colleagues, and also our internist colleagues. Right? Because a lot of the times we're talking about this topic, we're often talking about patients with decompensation. We're talking about patients that are sick, and we're talking about the concept of adrenal sufficiency and patients that are very sick,
- 00:25:26and consequently we're seeing patients in the hospital, and both are intensified, and internists play an integral role in this.
- 00:25:34So these are our learning objectives for today.
- 00:25:41So i'd like to begin with a case. This is a real patient we saw here two years ago, and we actually are continuing to follow. It's a fifty six-year-old man with a decompensate alcohol associate cirrhosis, who is amid for abdominal pain.
- 00:25:55He had a proper meld score of about twenty, and you can see on the left side of this chart here. These are his labs from a prior hospitalization. Three weeks ago pretty normal blood pressure kind of an average mild type of nutrientia, normal potassium level and a normal Crabney level.
- 00:26:12But on this presentation we can start to see that he's now has a new aki, and has a low album level.
- 00:26:24It's mill score is now twenty seven. He has this Aki, and it's notable that, despite this hypertension, he's actually been on alpation mitigrant for more chronic type of attention.
- 00:26:35So with this profile the astute medicine team studs. Wait a second. Could this be adrenaline efficiency, and they actually obtain it? A morning cortisol level
- 00:26:45it's like you're going to.
- 00:26:47I'll use this to sort of frame Today's talk and say, Does this patient have adrenaline's efficiency?
- 00:26:52And if so, what additional workup is?
- 00:26:54Well, Thank you.

vlk6a

00:26:57It's:

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00:27:01I think that's gonna help

- 00:27:03by now.
- 00:27:06Testing. Yeah,
- 00:27:08Yeah, I think we just need to mute the rest of them. Okay,
- 00:27:12here's the one that matters all right.
- 00:27:19Oh, so difficulties!
- 00:27:21There we go. Okay. So before we start, let's kind of review some of the basic physiologic changes in cirrhosis.
- 00:27:27I think many of us are very familiar with this. We see lots of patients with liver disease here, and we're well aware that in cirrhosis we develop horrible hypertension.
- 00:27:35We have splanking face of dilation, related to visitilitary substances released from the inflamed liver, such as nitric oxide, which leads to arterial underfilling which then regulates our reading and Angiotensin aldosterone system.
- 00:27:49Ultimately, as a result of these two issues, we get sodium retention, pause a volume expansion, and we get a dilutional hypnotremia.
- 00:27:57We also know that cirrhosis is an inflammatory state, and we get increased rates of bacterial translocation,
- 00:28:03and we also have systemic information going on, and so we can get spontaneous infections. But probably most pertinent to this talk specifically is that when the liver is inflamed and damaged, related to the fibrosis, there we get decreased synthetic function.
- 00:28:17And importantly, this leads to decreased production of binding calories that may be important for cortisol and adrenal function, including low levels of albumen low levels of cortisol, bonding globulin and low levels of high density lipoprotein, which is important because this is what transports Cholesterol to the
- 00:28:35So with that I'll turn it over to helmet right now to talk more about some of the underpid functionality.
- 00:28:41Thank you.
- 00:28:45Thank you, Brian. It's really pleasure to be here with you this afternoon. This is a very complex topic to discuss.
- 00:28:55It's still a evolving issue. Ah, how to diagnose and manage! Ah! Adrenaline sufficiency and cerotic patients. Ah, however. Ah! By the end of this presentation you would realize that there are some ah principles that you may have to do and follow. Ah! In order to make that diagnosis. Just before I start discussing some of the aspects of the normal
- 00:29:24cortisol production and
- 00:29:28the classic adrenaline sufficiency picture that may overlap with cerotic patients. I would like to point to
- 00:29:41these two. Um, let's see.
- 00:29:51Like to point to these two papers
- 00:29:57had out of press. Ah, one came out last week, and the American Journal, gesture and torology, and our steam. The colleague Ah Ryan, was the first author on this and the other one. Ah, just was published yesterday afternoon in the Ah Journal of Indigenous Society, and both of these ah
- 00:30:19papers practically explain some of the mechanisms that one may encounter invasions with adrenaline sufficiency and sort of patients.

- 00:30:30However, they also raise a lot of questions about how much we don't know about this issue.
- 00:30:38So if you think about cortisol. It's very vital for life. It actually contributes to a regulation of every cell in the world.
- 00:30:48Ah, um! That's ah explains why. Ah! Too much of cortisol, or too little of cortisol, may cause serious and ah fatal. Ah! Problems! In fact, patients with ah ah problems
- 00:31:05much higher mobility and mortality!
- 00:31:09Cortisol under normal conditions is produced in the adrenaline and the azona facilita, which is a middle layer of the adrial cortex.
- 00:31:22Ah! While the outer layer of the adrenaline cortex produced the metal which, going on the inner layer of the cortex is called zona reticularis. It's responsible for adrenaline and regions,
- 00:31:38and while the most inner layer of the other glands is called the Adrina Medola, and it's responsible for production of categories.
- 00:31:49Cortisol production is under very tight control of the hypothalamic pituitary, adrenal axis under various stimuli, such as day and night cycles.
- 00:32:05Ah! The hypothalamus reduces Ah! What we call a of typical drop in the releasing hormone or crh that stimulates betrayed land to produce Acth. And then Sdh stimulates cortisol and the adrenal gland
- 00:32:24That's our
- 00:32:26You realize that any problems with hypothalamus pituitary could also influence a cortisol production. Once cortisol is being reduced,
- 00:32:37there is what I call a negative feedback mechanism that will lead to inhibition and separation of Crh and acts preventing over production of
- 00:32:55There are, uh
- 00:33:01ah several ways. We can evaluate this axis by practically by measuring
- 00:33:17another aspect of the process of cortisol production is what we call adrenal stroidogenesis, and the two rate limiting
- 00:33:31factors that regulate cortisol production are The first one is called the
- 00:33:40stereogenic acute regulatory protein or star star is responsible for mobilization of
- 00:33:54the mobilization of cholesterol from the to the mitochondria Membrane thus might, upon their efficiency or abnormalities and might under function may need also to put this all the efficiency.
- 00:34:11The other important factor that's responsible for Ah stroidogenesis is
- 00:34:26but also as she is responsible for the expression of astroidogenic enzymes, and there are too many enzymes in the real cortex. All of them are influenced by Acth. Thus Ah! In individuals with acth efficiency they may have atrophied atrial gland, and also a severe reduction in the enzyme activities responsible over cortisol production.

00:34:59Cortisol is produced in a very unique fashion.

- 00:35:03It has a vulnerable activity. It's produced in a pulses one pulse every sixty to ninety minutes. It has a Circadian rail, its highest production. It's early morning, and as the day progress it decreases
- 00:35:23reaching it's neither about midnight
- 00:35:33important to check it in early morning doing it in the day may not produce the results or accurate results that you're looking for
- 00:35:46when cortisol is produced.
- 00:35:49Ah! Seventy percent of it is bound to what we call ah cortisol binding goblin, Ah! And twenty percent is bound to algebraic. Thus conditions that are associated with reduction in Cbg or Album Ah can give you a false, Ah! Low levels of ah plasma cortisol.
- 00:36:15Only ten percent of cortisol is circulating in a free form, and that is the active cortisol that you are interested in.
- 00:36:26Now, there are several ways we can measure. Ah, Cortisol, we can measure total glass, my cortisol, and this is a most widely available method to evaluate it. It measures the bound and frequencies all together.
- 00:36:44However, this is not the most accurate way, because, as I will,
- 00:36:49i'll tell you later. Ah, ah! It's influenced by a low album, and it's the influence of Pylo Cbg. But also interested by other hormones and drugs. For example, estrogen may increase the binding ah proteins leading to falls, so you may notice that the field is shifting toward what we call plasma frequency.
- 00:37:17Plasma free court is all ah is more accurate, more precise. Ah, However, it's not widely available. It's a sent out. Ah Lab, It takes some time to get the results back, maybe one to two weeks, so you are not going to really have the opportunity to react fast enough to the results.
- 00:37:39Ah! The urinary frequency zone is another way to measure frequent. Dissolved. However, we utilize it in conditions associated with ah increase for cortisol production. It's less helpful when you evaluate at the level and sufficiency just assembly, because it gives you an integrated value throughout the day Doesn't. Ah, help you at all to figure out. Ah, ah! The big ah cortisol production!
- 00:38:09Ah! Another way to measure frequent result is, sell. Every port is all it's available. We utilize it here at Uba. It's also sent out. Ah! However, the problem is not many. Physicians are familiar with the ah celebrity of these or ah measures. Ah! When you get the results, probably don't know what to do with them. Ah!
- 00:38:31An endocrinologist! We deal with this issue a lot of times.
- 00:38:38Now, looking back into the bath of physiology, of the adrenaline sufficiency,
- 00:38:45and we would realize that it comes in three different flavors. Primary education, efficiency. That's when the pathology lies in the adrenal gland, such as autoimmune, adulthood.
- 00:39:02Ah hemorrhage, and the other glands long tube destroying the gland. Ah, infections, gray, limited diseases, and so on. All of these destroy the adrenal glands. That's what we call primary adrenaline and efficiency. In this case you will see a much elevation of Crh! And
- 00:39:25ah! When the adrenal glands are destroyed, that's what I mean by that. It's a cortical ah adrenal gland! And ah! Thus there is a loss of all steroids, the loss of mineral cortex and the serum lots of cortisol, obviously, and was of the and the region. This is a very important issue,

because if you make a diagnosis of primarily and sufficiency, remember, in addition to giving cortisol replacement, you need to give mineral,

- 00:39:55and the secondary and sufficiency. The pathology lies in the beatituary glands, such as in hemorrhage, trauma, surgery, and so on. And in this case you will see a reduction in production. Low acth, However, Crh is elevated
- 00:40:14in this case. Ah! The ah reduction in cortisol is isolated reduction
- 00:40:32in a tertiary which are really very similar to secondary. However, the pathology lies in mainly in the hypothalamus, and the most of patients we see with surgery, and at the rate and sufficiency are related to atrogen, so patients may be taking steroids for good toys for a long time, and then they surprise both the hypothalamus and twitter.
- 00:41:00Ah! And then suddenly they stop taking legal cortexoids, and then the patient presents with a manifestation of adrenaline sufficiency. So ah, ah! The most common Ah, situation! That you will see with the tertiary is ah related to chronic steroid use.
- 00:41:23This is the most famous Ah! Patient with ah primary adrenaline sufficiency. Jeff Ah Jfk. Ah! He was diagnosed in one thousand nine hundred and forty-seven, with Ah Edison's disease. Ah! After ah when he was thirty years old after he suffered ah! Two collapses, one in one thousand nine hundred and forty-five, after a parade in Boston, and another one he was based in England.
- 00:41:51Ah! It took two years to make a diagnosis, but there insufficiency on him. The interesting part is that he hit the diagnosis from the public
- 00:42:03throughout his campaign, and the reasons and presidency of fear of people take it against him.
- 00:42:12So the most common presentation we see with
- 00:42:18adrenaline sufficiency is ready to go to immune, and the real life. Practically it's a lot of immune process leading to destruction of the total cortex.
- 00:42:27I mentioned other causes, so I’m not going to over them again.
- 00:42:48Ah! We don't see A big mandation only scammed in sesics is can be implementation only in primary advanced efficiency. Where
- 00:43:14ah!
- 00:43:16The way to diagnose a degree and sufficiency based on the in the process of the guidelines you should aimport dissolved somewhere sometime between six zero Am. To eight Am. This is the best ideal time. If plasma could resolve basically the three microvember Dl: then you have strong suspicion of advanced efficiency. And I don't say you have a diagnosis,
- 00:43:46because again remember the factors that may interfere with the total cortisol production, such as hypothalaminemia and the other factors that will falsely change the levels of total cortisol
- 00:44:01If you happen to see the Am. Cortisolism three, then you may want to do a confirmatory test, and this can be done by doing photosynthropin stimulation test, giving, which is a synthetic acth
- 00:44:18and measure. You give it a robinus, and you measure cortisol response at thirty minutes and sixty minutes.
- 00:44:31The normal response you should get greater than between micro Grammar T. L. Our increase in plasma cortisol.
- 00:44:41Ah, A.

- 00:44:43Again, you have to be really aware of the essay that's being used for measurements of purchase. Here at Uva we use ah immunos, and most of you may know. I say it. Ah cross over to some other recursive steroid precursors. So it's not one hundred percent act. If you really want to do accurate measurements, the utilization of liquid format, you might spec. Probably is a bit
- 00:45:12way. In. In fact, the slide showing Ah, when they used the label chromatography, mass spec uh the uh plasma uh total cortisol was about twenty percent less than what's measured by immune, I say, uh! So this is where the field is going, so we'll be seeing more and more sensitive, accurate.
- 00:45:36Um.
- 00:45:38However, I would also should say the diagnosis of Adrenaline's efficiency and the levels that I mentioned about the cortex and stem test. This has not been a validated invasions with Theeros
- 00:45:56right. So how may we go back to our case? Right? This patient was hypothetical.
- 00:46:02They were hyper nutrients.
- 00:46:04They were hypocalymic. They had a low-morning cortisol, and they have abdominal pain right? So we have a slam dunk diagnosis right?
- 00:46:11What? Uh
- 00:46:16on the surface? Yes, However, if you think about. Now I'm playing a role of
- 00:46:23if you look into ah nations with advanced-level physics they present with hypertension. They present with hypoonia. They uh present with an elevation of serum, threatening and un the present with Aki most of the crimes. Ah! Because of the hypothalaminemia they present with low ah cortisol levels total cortex of vehicles. Ah, they have a permanent date. Ah, also
- 00:46:53they mimic very much some clinical manifestations of a different affairs, so
- 00:47:01based on
- 00:47:04what you told me about this patient. I am a little bit skeptical,
- 00:47:15so I think, to helmet's point here right. We cannot definitively say that this is adrenaline sufficiency in this patient with decomposition, and I've been probably Mingemia.
- 00:47:25So I think it seems like some additional work that is necessary to agree absolutely. And this, looking back into the situation. When this patient was admitted to Uva, he had
- 00:47:39Ah, the hypertension, the hyper-calmia And elevated the syrup greeting in a baseline. A M. Cortisol was low point sex, so the additional work I would like to see at this time is the ah
- 00:48:02he had. Ah! The test done, and the patient's response was, Ah, submarine went from Lizanne Zero Point five at this line to eight point eight at sixty minutes. Remember the guideline states that you should achieve a team. The number eighteen micro Number Dl: in the response crossing the station did not achieve that. So this patient
- 00:48:32failed, or, I should say looks like failed control system. Test the reason, I say it looks like because the presence of hyper anemia, I don't trust the cortisol levels in this,
- 00:48:50so I think, as sort of helmet and I are alluding to. There's a number of different challenges that we have to overcome when we're talking about Hba access measurement and patients with services.

- 00:49:01All right. We've sort of hit on quite a bit that there's reduced binding globul and synthesis. We know that the synthetic dysfunction in Pyrhosis leads to low album and Cg. Levels. And thus there's questionable reliability of simply using total cortisol
- 00:49:14I think it's also really important for us to consider the context in which we're seeing this patient and assessing this patient right.
- 00:49:21What we know from current and prior literature is that the severity of underlying liver. Disease also affects the degree of synthetic dysfunction, and therefore the degree of hypovalmia and or levels of low Cbg.
- 00:49:35We also know that a lot of these patients with liver disease get infections, become septic and become critically ill.
- 00:49:41We also know that just in the general population patients with crept. Illness also have lower levels of albumen, and have decreased for Zalbani, globulin synthesis. And so it becomes hard to tease out what may be the effect of deliver disease itself, and what may be the effect of the degree of illness itself as well?
- 00:49:56I think there's some other units or questions as well. For example, is there actually differential loss in these patients of algorithm versus Cbg? We talked about that Cvg. Finds about seventy percent of the total of cortisol, whereas album is about twenty percent of that. And so if there's different losses here, how do we count for that? Are we measuring this really measuring the right thing.
- 00:50:16I'll point you here to this graph here. This is a study by dictal and all but other ah sites have sort of shown similar results that while there is correlation between these two levels, it's not a one-to-one right? The correlation here is only about zero point four, six. So you know, this is in a sort of an under-explored area.
- 00:50:34There's also a concept in the liver or hepatology world that we recognize that the album that's produced by this serotic liver may actually not be quite functional as album produced by a non-serotic liver and so is this album really is capable of finding cortisol as elders, And that's not your interesting question.
- 00:50:53Well, the other things we also know is that in patients with liver disease is that there's actually abnormal cortisol secretion and elimination.
- 00:51:01Our research has shown that there's actually reduced cortisol secretion,
- 00:51:04and as that's sort of seen here in this left chart, that we can see that patients with more severe cirrhosis. So this is patients with a child cute eight or more, so that the child do be. These are patients that are decompensated,
- 00:51:15and if we break it up specifically by the child Q. Score of A. Or our compensate patients and Beer and Cr. Comes a patients. We can see that this Csr. Max, which stands for cortisol secretion rate maximal, is decreased in those with more severe liver disease.
- 00:51:30Conversely, despite this decreased secretation of cortisol there's, actually reduced urinary elimination of cortisol as well, and we sort of see the same trend where the patients with more severe disease have actually decreased elimination. So it was potentially less production of it, but maybe it's not also getting reduced.
- 00:51:49I'm just saying the balance of This is also a non-explored area,
- 00:51:53as how we pointed out, Cortisol is secrete and pulsatile fashion, and displays a very unique pattern throughout the day.

- 00:52:01We know that in patients with liver disease there is a disordered sleep wake cycle, and that's been well-characterized in the ephatic and cephalopy literature.
- 00:52:10We also know that melatonin which is responsible for this is a hepatitically-produced hormone and so that may play a role.
- 00:52:18One of the interesting things was: This is a very small study by Sarah Montagne, and I publish about ten years ago. But this group actually looked at
- 00:52:26characterizing the for the pattern of cortisol secretion in patients with liberties, and they looked at both nations with Koppus, a disease which is shown in the dark line here
- 00:52:39over the course of twenty four hours, and they also looked at patients with decommissioned disease. In this sort of gray mark. Here. They can sort of see that, as tell me, said Right, most patients P. Cortisol level is around six to eight Am. And we kind of see that in that dark bar which is our compensate patients,
- 00:52:54but those with decompensate cirrhosis We sort of see this later peak kind of more in the eight to ten Am. Range. And so if we're measuring this cortisol level at maybe seventy eight Am. Are we simply getting a falsely low level in some of these patients decompensates for us.
- 00:53:09This obviously needs to be validated in much bigger studies, but I think this is sort of an interesting hypothesis here,
- 00:53:16and then, I think,
- 00:53:17one of the big elephants in the room. It's still A very debated topic to this day is what we call critical illness, really corgo and steroid insufficiency, or Circe.
- 00:53:25This originally was called relative adrenaline sufficiency back in two thousand and two. When a French group kind of defined this phenomenon. But it's been kind of a hotly to be a topic in the critical care, literature,
- 00:53:37and the regional concept was that this was a lack of adequate, substrate to match the physiologic demands. In a stress state
- 00:53:44it's become a lot more complicated, and the has been muddied since then with additional literature. But This is kind of the basic underlying concept.
- 00:53:51And in this literature, instead of using that peak, total horizontal level of eighteen as being our diagnostic threshold, they actually used sort of a circuit measure of adrenaline responsiveness by looking at the change in total cortisol level of less than nine as being diagnostic For us.
- 00:54:07One of the problems we know as I talked about before, is that critical illness also leads to low album in levels. And so are we sort of falsely getting patients with low levels and less responsiveness.
- 00:54:18We also know independently that look cortisol, bonnie globulins are proportional to the love of illness, irrespective of whether patients have liver, disease or not, and this itself predicts short term mortality.
- 00:54:28And in this phenomenon we know that there's a dissociation between acth levels and cortisol levels right? The kind of classic teachings that patients are really sick, or try to maximally stress their adrenaline tries to pick up, and they should be sort of secreting, you know, maximum levels of cortisol.
- 00:54:44This sort of classic figure from Boone in all in two thousand and thirteen in the New England Journal kind of showed that patients did have increased cortisol levels compared to

controls. As this kind of blue bar is the intercortile range for patients that did not have critic illness.

- 00:55:00But we sort of see that right and patients that areatically stimulated. You normally would be thinking that the Acth level should be high kind of stimulating the adrenal gland, and it actually wasn't it was actually lower than average. There's some thought that this may be related to reduced cortisol elimination. But again, this is sort of an area under investigation.
- 00:55:17So with this in mind, i'd like to sort of reframe The concept of adrenaline's efficiency, or probably more likely, a better term is adrenal dysfunction in patients with cirrhosis.
- 00:55:27So this was first talked about in two thousand and five by Paul Merrick at all down the road, and he took a cohort of patients with prick and illness in cirrhosis and sort of saw this critical illness-related chord of steroid and sufficiency. He called it. This kind of sexy term the hepato adrenal syndrome.
- 00:55:45It's been later described in the non critically Ill patient. But the problem is this: is such a heterogeneous group, right? I mean, if you think of the patient with cirrhosis, you can think of the person that's walking on the street, and doesn't know they have it, or you can think about our patient with Meld forty that's actively listed to transplant, and you know extremely jaundice. So those are two very different patients.
- 00:56:05And so that becomes a problem. Because how do we define really how common this is in the response to this? So to try to sort of answer this question. Our research group started looking at this in a meta-analysis form,
- 00:56:19and so we looked at all the published studies. And so there are twenty two high-quality studies that looked at this and overall the prevalence was about thirty, seven, and that's across all groups all different ways of measurement, all different thresholds. But just to get a general sense,
- 00:56:33as you'd expect the more severe liver disease, the more common this phenomenon is
- 00:56:39the type of testing matters. Now we talked about. The typical way we test people is by giving them a huge two hundred and fifty microgram dose of acth. But there's actually a low dose test out there of more than one microgram. And so if we're giving them a lower dose, you'd expect the prevalence may be higher.
- 00:56:55Now, importantly, I'd like to point you to this kind of box over here how we actually diagnose this adrenal dysfunction. So if we use the kind of general population criteria of less than eighteen milligrams at a peak Level prevalence is about thirty percent.
- 00:57:11If you look at that change in the total cresal level. So that does these reunogen respond to at least nine micrograms per jest leader over baseline. It's a little higher about thirty six percent.
- 00:57:22But, as Helmet said, You know, plasma-free cortisol really is the sort of most sure way to measure cortisol that's independent of those bonding glide ones. And so, if you look at precursor levels,
- 00:57:33the prevalence of this adrenal dysfunction drops rapidly down to ten percent
- 00:57:37again. Because maybe we're not getting interference from these low binding login levels.
- 00:57:43And interestingly, though, if you look at whether these are stable, outpatient, or hospitalized patients, but not grip L. The prevalence is somewhat similar which could suggest that there's contribution related to the underlying liver disease.

- 00:57:55I think one of the other things that's important is that this hasn't really been cited in longitudinal fashion. Right? So we don't really know Is this just a simple or just function related acute illness? Or is this actually a like a permeating condition? Um related to that liver disease that may not resolve as soon as the acute illness is is occurring. There's actually been only one very small subgroup analysis of eighteen patients from a study in two thousand and thirteen by Oscar data that looked at this
- 00:58:19and patients that were hospitalized, sick, adrenaline sufficient by the criteria that they used.
- 00:58:25Then they re-measured it three months later, when they were presumably healthier in the outpatient setting, and they did note that most of the patients did have reversal of this phenomenon. But again. This needs to be validated in a bigger setting.
- 00:58:38So let's go back to our case.
- 00:58:42So this was someone with abnormal total cortisol response to Ac's ecth stimulation?
- 00:58:48Because of this they were given this provisional diagnosis of adrenal sufficiency, and started on hydrochords on supplementation in sort of a typical fashion
- 00:58:57interestingly their symptoms approved pretty quickly, and during the hospitalization, and they were discharged along the
- 00:59:04so Ah!
- 00:59:06In the meantime the lab did a frequent zone
- 00:59:14also measured blasphemy, Ch. The.
- 00:59:17And, as you can see, blasphemy ch was thin, which is in the lowest side, and the frequencies all went from Baseline zero Point zero, five, four to at sixty minutes. One point, one, four, five.
- 00:59:36What does it mean? How to read these numbers? First of all, the baseline,
- 00:59:43despite having low plasma, free courts or a city at Tuslan. So you right away. You think this is a multi-factorial problem
- 00:59:56ah the between your gland is not able to cope with the reduced cortisol production, the expectation is to see much higher recitation. So this is
- 01:00:11may suggest that impatience with cirrhosis. They may have also a problem with the pituitary gland, reducing a
- 01:00:21second.
- 01:00:22The despite that the patient responded to cortex and stimulation test. It was not the level that we expect. One point. One, four, five
- 01:00:41is slightly less than what has been seen in normal individuals. Usually it's about one point, one nine, so
- 01:00:50it's its response, but not a maximum response. So based on these numbers, I would say there is some degree of dysfunction at both pituitary gland, and probably at stratogenesis,
- 01:01:14since the patient improved and the treatment was discontinued.
- 01:01:21I um
- 01:01:23hoped that patient
- 01:01:26will continue to improve. However, the surprise was once the patients discontinued, the treatment he developed the manifestation against of adrenaline sufficiency.
- 01:01:40And so with that right, you know, symptoms Again, that could be consistent with this, some testing that's is potentially suggestive of this. And so this hydrocarbon was simply

restarted, and that you actually improved again. Kind of letting us to think that maybe you really did have arenal sufficiency,

- 01:01:57or at least adrenal dysfunction should talk about
- 01:02:01all right. So we kind of talked about how difficult adrenaline's efficiency is to diagnose in the patient's cirrhosis really But as clinicians. Ultimately, at the end of the day is the box stops here right? Why do we care about this?
- 01:02:12Well, I think first and foremost it's because it's associated with increased mortality, and it's increased mortality independent of the Meld score. So we know that in several studies that looked at adrenal and sufficiency in patient's cirrhosis. There's increased levels of mortality in that hour, and icu stay with an odds or issue about eight.
- 01:02:33Again, in the non-curricularial setting which again, is a very heterogeneous population. It's a little hard to tease through this. And so our research group tried to do this with this meta-analysis. We talked about and looking at our forest plot. Here
- 01:02:46there are four studies that met criteria, and looked at the same sort of outcome of ninety-day mortality, which again, if you think about our metal score rates predicting ninety-day mortality. Again, it was originally designed after tips, what we now use as a surrogate and just sort of all in all settings,
- 01:03:02and we can see here that the odds ratio for patients that did have a dream. Sufficiency was actually close to three. So these patients that have it. It does tend to pretend a worse prognosis. And so maybe we should be thinking about this and diagnosing this more. If this is something we can potentially intervene on prior to transplant.
- 01:03:21There's also this concept out there that maybe this adrenal insufficiency is actually more of a like a a true organ dysfunction akin to what we see in our patients with decomposition Cerosis that present, and have what we call aclf or cute on crying, never failure.
- 01:03:36We know that the patients in acronymic liver failure and different flavors have a significantly worse prognosis. But interestingly, there's data from this Italian group by piano at all two years ago that actually showed that patients with adrenal sufficiency had similar to potentially, maybe even worse prognosis
- 01:03:55compared to those with more typical acl criteria compared to those without it. So again, this seems to be validating larger groups. But I think it just shows that potentially we're missing something here that would potentially benefit patients by earlier diagnosis and potentially earlier treatment.
- 01:04:12So really, what might cause this in cirrhosis I think we sort of allude to the fact that this is probably a multi-pronged cause.
- 01:04:20What we know is that the increased inflammation in cirrhosis leads to the up regulation of a pro inflammatory cytokines,
- 01:04:28and that's really both from the liver. It's self-producing these, but also the bacterial translocation producing these these pro-flonentry cycles can directly down regulate pituitary and hypothalamic hormone secretion as well as exert direct effects on the metabolic art. Sorry the stroogenesis and the adrenal gland.
- 01:04:48We also know that relate to the decreased synthetic function in the liver was actually decreased. Production of this enzyme, called, Let the same cholesterol asyl transfer ice or lcap.

- 01:04:57This is ah an important enzyme that actually modifies those cholesterol molecules into what we call cholesterol esters, and those are actually important building blocks to form that mature hgl particle right?
- 01:05:09An hdl particle is what gets shuttled then to the adrenal gland, to then get incorporated by the protein, that star protein in the mitochondria to then start the stereogenesis. So we're having decreased production of a really important enzyme. We're having decreased levels of htl. Maybe we're having decrease for kind of trafficking of the important adrenal substrate.
- 01:05:28Um, So that could be a potential mechanism. As well
- 01:05:35help me talk specifically about the adrenal gland.
- 01:05:39So in that patient that we I just reviewed with you there was two levels of dysfunction, one as a pituitary which we really don't know exactly why.
- 01:05:55Probably a being sick inflammation maybe plays a role there. Ah, but at the level of that real gland. There are several ah possible explanations. One is related to enzyme deficiencies. Ah! We know from a small number of applications that inflammatory cycleines can actually decrease the activity of these enzymes leading
- 01:06:25to reduction in adrenaline stereogenesis. But also there is a good possibility that there is also mitochondrial abnormalities
- 01:06:38that prevent the incorporation of cholesterol. Ah, ah! Into the ah stereogenesis! Ah process similar to what I just mentioned about the star protein that
- 01:06:53uh transport the uh cholesterol from the outer mitochondria member into an mit. So um! All of this really is not confirmed, I have to say, Ah, we have to look carefully into. Ah, ah! These issues again! And the Brian actually is ah doing some of these studies. Looking into the pictures of some of these steroids trying to define which enzymes are influenced more, and which ones
- 01:07:22are influenced by, let's say the liver disease,
- 01:07:36so which patients really may be at risk for this.
- 01:07:43So I think by now we sort of realized that patients with decomposition, disease, high Mel child pew scores severely ill patients, low album levels of hgl levels all kind of are these risk factors for us? The problem is right. These are all co-linear things. They all happen together in a lot of these patients. And so
- 01:08:01from just being in clinician sense, you might think, Ok, I'm seeing all these patients. But how do I really narrow this down? The answer is, it's hard.
- 01:08:10So when we think about the presentation of this, there's not really any good established criteria on whom to evaluate. We talked about that many of the signs and symptoms overlap with decompensate liver disease.
- 01:08:21But I think there's some kind of hopeful tips to think about this more recently in the patient. You're seeing on a routine basis.
- 01:08:29I think we all know that in patients with critical illness, ref factory hypertension, we tend to think about this more related to crooked illness. But again, if they have liver disease, that maybe they may also have that factor as well. I think it's important to know that an unexplained or severe hypernutrimia,
- 01:08:47particularly the absence of large volume societies and holding diuretics that we need to really think about this.

- 01:08:54I think also in the fact of patients that have unexplained, and a persistent hybrid tension relative to baseline, especially if they Don't, have a known or or recent diagnosis of Halloweenal syndrome that this needs to be considered, and I think in the patients we're seeing with very, very low Hdl levels, particularly when are not critically ill. We need to be. Think about this. There are some studies, including some of our own work that have shown actually levels less than fifteen, and specifically less than somewhere in the seven to ten range that up to ninety five percent of these patients will actually have an up here response to the stem test.

Unknown Speaker

01:09:27So that being said, How should I really approach testing?

- 01:09:33So there is no
- 01:09:36clear guidelines or guidelines on diagnosing adrenaline sufficiency and cerotic patients.
- 01:09:44However, we can adopt based on what's published
- 01:09:51the first of all measurements of the baseline plasma, free cortisol, and acth would be important, followed by a
- 01:10:06I'm. Now focusing on patients with adrenaline with livers, the measurements of frequencies, all would avoid. They have a hypoagrominemia, hypo, or decrease Cbg. But again, you need to be aware that it will take
- 01:10:27one to two weeks before you get the results back. You can also do the celebrity cortisol.
- 01:10:44However, if you look into the correlation between the three cortisol and the total cortisol. The correlation is not that robust? So you cannot really
- 01:10:55figure out. The frequency is all just based on what you're looking at. At the of Cortisol
- 01:11:03again. We don't really have a guideline how to read these numbers in patients with
- 01:11:14now. Uh,
- 01:11:16there are some consideration to think about when you think about diagnosing adrenal dysfunction in Soros First of all,
- 01:11:40Ah! Be aware of the essay that's being used. The best, I say, is again, is utilizing the Lc. Mass. Spec. I say.
- 01:11:53Ah, there are some controversy about using the Delta increase in ah cortisol levels after controls and stem tests. This is a very sticky area, and I'm not going to confuse you with it. Personally, I'm not yet
- 01:12:11convinced. But maybe in the future we'll see something else
- 01:12:18again. There are several questions a person may ask, What time of the day should we do? Stimulation? Just? We don't know.
- 01:12:28Ah, what's The effect of illness is severe illness, equal mild illness. Ah! With severe illness, influenced the results of control system We really Don't know. So we are still
- 01:12:44walking through
- 01:12:48a field that's still evolving, and

- 01:12:52um one more, a couple of more issues that you need to be aware of. You may hear about, load those acth stem test that's practically using instead of two hundred and fifty microgram tests. You use one milligram test uh a microgram. Test
- 01:13:10the uh, the uh, the low. Those test is not as accurate as uh in in in in sickness, because it may uh over diagnose. So I wouldn't recommend the low doors. It's also technically challenging.
- 01:13:29Um!
- 01:13:33How should I treat
- 01:13:36patience with? I didn't, and this much
- 01:13:42so, I think you know one of the important things kind of being to sort of The of this matter is that
- 01:13:47if there's very clear evidence that this patient may have true adrenal sufficiency that they're, manifesting a lot of the primary symptoms between like hyper-pigmentation and
- 01:13:56and things in there. Liver disease is pretty well compensated it's pretty non-controversial to treat that
- 01:14:03but I think we've sort of trying to convince you today is that there's a lot of gray areas here, and a lot of these patients have some degree of dysfunction. But the question is really is this something that really warns treatment? Because we talked about before the patients that do have abnormal response to the skin test do tend to have worse prognosis.
- 01:14:21So it,
- 01:14:22the long short of it is Honestly, steroids have only really been studied in patients with critical illness. In this field
- 01:14:28there's actually only been about four good quality studies of looking at this, and similar to the priceless literature in the general population. The evidence is mixed on their efficacy right where, as you may expect, there's decreased levels of vasopressor doses and increasingly of us for free days and a better shock resolution. But this comes at the expense of issues like gi bleeding kind of no real effect on icu survival, and potentially a signal that there may be increased risk of multi drug.
- 01:14:58These patients are typically given Ah, typically what we call stress doses. So somewhere in the range of two hundred to even upwards, upwards of three to four hundred milligrams per day of hydrocortisone
- 01:15:09In Nonetheless, there's not been any studies, both prospectively or retrospectively, that have looked at this issue,
- 01:15:16and so I would really only recommend routinely giving replacement in consultation with hepatology and endocrinology. And really, if there's concern that the patient's presentation at hand cannot be explained by anything else except potential dysfunction.
- 01:15:32Um as potentially in this patients, you know where we give um steroids. They improved. We thought, okay, we thought a lot about this. We took it off, and then their symptoms returned, and then they improved afterwards. So that is a kind of the patient that maybe benefit from this.
- 01:15:48One of the other issues we we know about um is that the optimal duration of therapy is unknown. Right we talked about is this sort of a static phenomenon? Or is this something that's more dynamic related to the illness that's unknown? Um. And so, if we do treat this patient, we can try to taper like we did in that patient we talked about in our case,

- 01:16:06and we can stop and sort of see their effect. It's also, unclear, whether we should actually be retesting these patients down the road. The jury's out on that.
- 01:16:14But but that's something for virtue, investigation,
- 01:16:19One of the things as a transparent appetologist here that always comes to mind is right. Okay, the end of the line, right? What I want to do for this patient is try to get them a transplant, because we know that's going to fix a lot of the underlying serotonic physiology and other broad retention Manifestations for having
- 01:16:33the literature assumes that this is the definitive treatment for this adrenal dysfunction right? Because we're sort of taking away all that serotonic physiology that may be associated with this. But the problem is, transplants sound to panacea, because there's a lot of issues with access to transplant. In addition to this, just the general uh are the eligible for it from a medical or surgical perspective, and just the general weightless issues really into supply demand.
- 01:16:58The other interesting phenomena is that most of our immune suppression. Regiments include a large dose of steroids right at the time of transplant, and then a gradual taper, and we cannot assess the Hba axis accurately for sort of giving someone hydro steroids at that point.
- 01:17:13Probably the most interesting question, Right is, Does adrenal gland. This function persist after transplant?
- 01:17:18The answer truly is unknown, because this really Hasn't been studied, or and people haven't been routinely tested afterwards.
- 01:17:24But i'll give you like from a clinical perspective. The answer is probably no, because most of these patients end up bringing off corcosteroids somewhere between one to three months after transmit for a liver, and we don't routinely test for this, as we sort of talked about, so presumably this is an organ dysfunction that gets resolved.
- 01:17:44So, going back to our case, this patient was ultimately transplanted six months later, and the induction steroids were tapered to the prior. Had reporters in dose.
- 01:17:53He actually followed up with the end of the
- 01:17:56so uh,
- 01:17:58unfortunately, a happy ending for this patient after Sun's plant. This patient had a normal cartoon stimulation test and a lone on. So it looks like whatever he had this function, or between the dysfunction, has resolved, after
- 01:18:25so good news for that patient right?
- 01:18:28So for just some final take on points,
- 01:18:31you know, I think hopefully, we'll convince you that adrenaline's function is common in patients with decomposed liver disease, but really requires a thoughtful assessment. And there's a ton of gray areas still out there.
- 01:18:41I think it's important to know that patients with cirrhosis and adrenal dysfunction have increased mortality independent of that melt score. And that's really why we're talking to you about this today. Because this is something we need to be thinking about on a more routine basis.
- 01:18:53However, we really need to exercise caution when we're interpreting total course, all levels and cirrhosis. Specifically, I think one of the biggest clinical pearls. I think that's helpful is

to really avoid using an isolated morning cortisol level as sort of a surrogate measure, because even if it's low in the space and population

- 01:19:09that could just be lead to their underlying synthetic dysfunction and low levels of Cbg and Albumin, and it doesn't actually predict response to stem testing in this.
- 01:19:20And thus we really do need to send these patients
- 01:19:23that there's really a lack of appropriate uh changing cortisol after you. Cg. Stimulation may be the most informative, but this is pretty controversial. And, as tell me, said before, we really need to figure out what really is the best way to interpret the stem test results. And what's the threshold. In this space of the population,
- 01:19:40and ideally free crescent levels are very helpful, but sort of help us more down the road to form a holistic picture, and are not really to be used in an immediate bedside setting. If there really a suspicion for this patient having adrenal dysfunction, we need to treat it immediately, and then sort of figure out later.
- 01:19:56Ultimately, this is something that really needs to be multidisciplinary between the Internists intensivists, hepatology into endocrinology, because ultimately This is something that may persist in this patient prior to transplant.
- 01:20:09And then, of course, more research is needed.
- 01:20:12So with that I'd like to thank you guys all very much for your attention. I'd like to thank Dr. Gudnick and Dr. Bongol for inviting us today. Um! And of course, the rest of the committee for, uh helping us talk here and then to the rest of our colleagues, both in our division and our research group. And of course, all the wonderful residents and students that have worked with us through the years.
- 01:20:32So with that, thank you again, and happy to take any questions
- 01:20:50if yeah,
- 01:20:54it's up to me.
- 01:20:58That was very thought for me. I'm so glad you stayed with us. You said that patients that you should think about treating or testing
- 01:21:10you eliminated patients that already had a diagnosis of Hrs. I'm. Seeing you see about Hrs a lot during your talk, and from the resin point of view those patients often look very much like adrenaline sufficiency patients, and I don't think I've ever undergone the work up for an Hrs patient. But I've had a lot of patients that were treating. And to be honest in those cases,
- 01:21:31let's we're not totally sure what we're doing. It's usually not going well. Should we consider Ai a diagnosis to exclude before we give an Hrs diagnosis a diagnosis. Exclusion.
- 01:21:45I think that's a great question.
- 01:21:48The short answer is, we don't know, I think a little longer answer is that in those patients the physiology and the clinical manifestations can look similar. I think we know
- 01:22:03it was a lot more research on Nhs and the therapies for each rest are a lot of a lot more evidence behind it. Although again, as we know, the reversal of interest. Success is not that great, especially with our currently available therapies? Although Turtle press, and may finally be approved in the near future,
- 01:22:19I would say, if the patient I don't think we necessarily have to always
- 01:22:24evaluated a patient for this before starting therapy, because we know that the renal dysfunction without me it

- 01:22:33therapy it directed towards it, and trying to reverse the underlying physiology is associated with exceedingly poor outcomes, and so I would never want to delay that patient's potential therapy. Um, I think if the patient has other manifestations, including, you know, things like abdominal pain, if they're not responding initially to some of the um you know album in mid-rinth, that may be a situation where maybe we start to think about that as an adjunct
- 01:23:01potential organ dysfunction. But I would I would say to sort of focus definitely, initially on the Hrs physiology
- 01:23:09a great question.
- 01:23:14Thank you. So thank you both so much for your talk. Um! Could you speak a little bit to the the role for mineral equipoid, um supplementation, and serosis? Knowing what we do about a lot of the therapies that we have with Mras um, and how that plays a role in keeping people stable.
- 01:23:34So, uh
- 01:23:35for mineral requires receptors to work the need to look at it so patient-efficient in cortisol?
- 01:23:46Will don't respond well to prisoner agents, or fluorine which is an enzymatic mineral protocol. So you want to make sure that cortisol is expressed before you will see any improvement in
- 01:24:03um. Ah! Short of that! Ah, really, we don't have ah enough information to say Ah! In various patients we have a mineral deficiency most of the times. What you are seeing is a visa dilation based on visa dilator hormones reduced by inflammation and ready kindness, for example,
- 01:24:22so a court is always still a major issue here. If you are going to treat hypertension, for example,
- 01:24:34I thank you, but both for your wonderful talk. I have really more of a comment, I guess, and that is that many of us. I actually welcome feedback on this.
- 01:24:45A more general comment about testing in the coast and treatment stimulation tests. Many of us are adopting a lower than eighteen threshold. The eighteen is the threshold in the guideline.
- 01:24:55You showed a paper from Dr. Bradj Vorski, who, in fact, was a resident here. They didn't to test our specific essay. But Mark Gordon at the time was One of our wonderful clinical chemists said that the characteristics of our essay are similar to the Our immuno assay are similar to the immuno assays. They tested,
- 01:25:15but suggested an appropriate cut off might be fifteen instead of eighteen; but Dr. Culver, who
- 01:25:22he left and left me out to hang to drive. He mentioned a much more recent paper just within the past month or so that did specifically test our assay and the cup they're suggesting it's not being less than eighteen. I'll see if you can send that to u

Unknown Speaker

01:25:37you know it's just a comment that when you do a cosinerop and stimulation test eighteen is probably too high with our modern essays, and it may be fifteen or fourteen.

Unknown Speaker

01:25:45Weirdly, yeah, totally agree.

- 01:25:52I think an important correlate point to that is again, these reference ranges and sort of the
- 01:25:57the evidence that these studies are based on are based on a general population too. So they're not necessarily cirrhosis-specific so they're not always accounting for the bonding blob and deficiency.
- 01:26:07Do you know, if anyone's looked into associations between uh drain, old as functionerosis and spurs l anemia, since they both have to deal with cholesterol processing.
- 01:26:18That's a great question. So
- 01:26:20the answer is, Yes, we've so
- 01:26:24so Dr. Caldwell here, one of my colleagues and many of you guys are familiar with had this I actually had that same question a few years ago, and he and I looked into this
- 01:26:35sort of some unpublished data. And so our theory was, yes, that because for cell anemia is essentially a hematologic issue where you have deficient assterified cholesterol within the membrane of the blood cell, you get sort of laxidine deformity, and it's much more likely to lice
- 01:26:52whether that's related to this. And so we don't have enough data yet to say definitively, The there is an increased
- 01:27:01presence of spurs cell anemia in these patients that do have adrenaline sufficiency. But whether you know the exact molecular mechanism,
- 01:27:13and specifically whether that predicts this, we just don't have enough data yet at this point. But yes, I think um in patients that do truly have high levels of spurs. They anemia So in the literature, you know, so highlight, hybernous for cellular sp cells is in five or five or high-power field.
- 01:27:32Um, those patients may be someone to think I would. I would add that any condition associated with increased himolysis. But the adrenaline and at risk Ah, adrenal is very vascular and very easy to ah get his chemical.
- 01:27:48Ah! And also we see a lot of ah micro ah plots! Ah! In the Adrian glands in those individuals, so any condition associated with him increase himolysis. But the real interest,
- 01:28:03the question for the chat all right here for my understandings for a lactone Correct me if I’m wrong increases cortisol levels. Thus, when we stop spono and acute illness, could this possibly lead to a secondary adrenal insufficiency,
- 01:28:22should we account for the use of this agent in the evaluation for adrenaline's efficiency or spyron? Lettone practically go up the minerals code receptor and to my knowledge, it doesn't influence directly. Cortisol censuses.
- 01:28:41Ah! Mineralical stories by themselves have a very weak glue
- 01:29:00or high levels
- 01:29:02can crossover to stimulate them on the protocols. So, uh, to my knowledge, there is no direct relationship between spyron Lecton and uh Excess Co. Dissolved production. Probably the illness by itself can dissipate, and a major role in increase. Ah, of course, is all on those individuals. But directly I’m not aware of any.

- 01:29:31Oftentimes in the make you, we use stress to steroids for patients. Um like some big shock who aren't just responding to. But I've encountered many patients with cirrhosis who are just hyper-tensive and have escalating pressure requirements. I was wondering if um stressed. Those steroids have been validated in patients with
- 01:29:50So there's been about four or five studies looking at that. And
- 01:29:56you know there's sort of mixed data on it, you know. It does tend to improve the
- 01:30:01um, raise our repressor requirements, but it can cause, you know potential issues like I'd point out, gi bleeding and potentially infections. It also doesn't seem to improve mortality. And so
- 01:30:16you know it's. It's also sort of hard to tease out again with these patients of cirrhosis. Again, is this just the correct illness phenomenon? Is this their underlying adrenal dysfunction from the cirrhosis? Is it probably a combination of all. I think one of the other things that we know from patients with critical illness
- 01:30:32is that there's multiple issues going on one is that they have actually decreased cortisol eliminations. So they may actually be hypercortisolimic. And so you're just basically giving them a ton of extra cortisol that they're not fully eliminating,
- 01:30:47and also but because of all that inflammation there's actually a tissue-level resistance to that glup ofcuricoid and so that's some of the theories out there about Why, it may not always help,
- 01:31:00you know. I think if there are other indications in the respond, if they, if you do trial, stress or stereotyping, there is a response. I think it's fine to continue, but it may not be the panacea for everyone.
- 01:31:11I think one of the major controversies is to ask, is the article zero. It's helpful in very sick, and a lot of studies have
- 01:31:26has been have been done and showed that there is no really benefits of giving records and very sick patients. I mean, the outcome was no different than those individuals who did not get the three.
- 01:31:42So you have to be very selective, and probably this disease select the pulse. So patients with theerals may different from patients who have a severe semia, for example. So you have to be careful.
- 01:31:58I think also, just to your point, too, that a lot of these guys in groups they're very heterogeneous, and so they didn't look at all necessarily all these subgroups of those with that, et cetera. A lot of the subgroup analysis were based on those that
- 01:32:10had a response basically to the to the steroids, or we're looking, you know. And they looked at, you know, responders, basically or non-responders. But they didn't look specific at disease etiology. So I think that's where we're going with that question, and it's a good question. But we don't know
- 01:32:35very long. Walk up over there. Thanks for your talk, you guys, this afternoon. I was just curious thinking outside of the icu on the floor and in the outpatient side setting
- 01:32:45um patients with cirrhosis. Often we know that they have lower baseline mean arterial pressure, and we sometimes are happy with that as their baseline. But, um, and oftentimes when people with cirrhosis do have lower maps, we tend to use midterm as kind of a first line agent.

- 01:33:01Is there any utility or evidence behind thinking about adrenaline sufficiency and cirrhosis as a reason for hypotension, when there isn't an underlying infection or volume depletion, and thinking about doing gluccorticoids in addition to mitigrant or just Mediterranean itself, for I mean, I think that's a great question. So it's one I often ask myself in clinic. The answer is, No, there's no evidence for it, and that's just simply because it Hasn't been studied.
- 01:33:32I think you know, in the absence of other kind of potential features. If we're just talking about isolate hypertension in the in the major, and fixes it. I think that's fine, and I don't think we have to routinely study this.
- 01:33:45If there's other evidence that the measuring they're on that's going to go through the midterm. They're still hypotensive. Maybe they have, You know, hypov nutrients that that seems out of proportion to the degree of Say, That's where I think I start to think about it.
- 01:33:57You know, I think, until we sort of know more about this phenomenon, and have better ways of sort of predicting exactly which patients may be at risk for this.
- 01:34:06Um, I think it's not necessarily the first thing I think of it, but it's sort of like the My next thing I think of, you know, down the road we know about the increased basal elevators in deliver cer roses. Ah! And because of that, in fact, there is a lot of
- 01:34:24to show that increased cetacola means when leprosy is associated with decreased introvascular volume. That's what Brisbane.
- 01:34:34The reduction of blood pressure in that situation there is actually a significant increase in cascular means. But Tetacola means cannot work Well, in the absence of
- 01:34:46of course it's all in in addition. Uh, the really energetic activity is significantly increased in this condition. So you have enough based on constrictors, but actually it's caused by a lot of
- 01:35:04Ah! So the disease pathology is not clear. Cut it's a visible dilation only, but also there are basic constructors that are not working on,
- 01:35:16I think, just to sort of add on as well. One of the other concerns out there, too, is that if we just, if we start giving patients stereotypes, we don't have evidence for it. What's the potential risk? Right? So we know from patients, for example, alcoholic hepatitis
- 01:35:32that giving patients steroids there's an increased risk of infections. And so you know, one thought is that without clear good studies to show that this has definitive benefit. I'm always a little hesitant to start a therapy.
- 01:35:53No more questions,
- 01:35:55thank you.
- 01:36:06Just so that you see
- 01:36:12I have a question. But I have a question, but same share of the question. But I just want you to see this. Oh, thank you.
- 01:36:21Yeah,
- 01:36:26yeah, that's true. And then I’m in the good job.