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TRANSCRIPT - GR 04 29 22 Grollman Lecture - "Phillip Liverman Lectureship - "Acute Kidney Injury in 2022" ***Anupam Agarwal,MD,*** **from the University of Alabama at Birmingham**

UVA Chiefs

- 00:27:46Right well welcome everyone and a warm welcome to Dr Adderall to be getting a series of letters and lecture.
- 00:27:53After after all, is the executive vice Dean at the University of Alabama Birmingham school of medicine to be under sent and dogs here and nephrology and professor of medicine and the division of the prodigy if you're a doctor Adderall completed his training at the.
- 00:28:13graduate Institute of medication and research and Chandigarh India, the University of Minnesota and the University of Florida after all after completing has hypertension and.
- 00:28:24fellowship you ever see a Florida join the nephrology faculty and rose to the rank of associate Professor.
- 00:28:30In 2003 after a distinguished career, and for that she's going to division of nephrology at uab.
- 00:28:36And the Birmingham VA medical Center for you, since risen to the aforementioned endowed chair position, as well as the vice Dean position within the school of medicine.
- 00:28:44Dr Admiral is the principal investigator co investigator for several in a NIH funded grants focused on kidney injury, including grants that focus on the lymphatic system and its role in kidney inflammation and on the role of mana nuclear fatness.
- 00:28:59pathogenesis of a Kanye West credible among all has grants for this work is the principal investigator for the USB.
- 00:29:06ucsd O'Brian core Center for a car research facility that provides resources and expertise to cultivate high caliber multi site collaborative research from Ikea.
- 00:29:17Today, Dr Agarwal will take this significant research experience and combine it with this long standing clinical interest in a care.
- 00:29:24To give us a comprehensive review of the epidemiology pathogenic pathways and treatment strategies for you guys we're very pleased to have Dr Admiral joining us in person today, Dr Andrew Weil, the floor is yours.
- 00:30:06Thank you for that introduction and thank you for inviting me to visit Charlottesville and uba for this Lieberman lectureship i'm truly honored we've had a.
- 00:30:16most amazing time since that yesterday visiting but the division some numbers across campus as well, so thank you so the next 45 minutes or so i'll share with you some you know really a background and acute kidney injury, where we are awaiting being angry and going.
- 00:30:36So these are my disclosures none of these are relevant to the talk today.
- 00:30:42i'd like to regain recognize that Phillip Lieberman, this is a picture from his fellowship days, so you can see, you know youthful really take it away.
- 00:30:50too early from her you know untimely death and you've done some nice work in a really bad time in 1980 he published this paper, showing that he asr or.
- 00:31:02recite sedimentation rate actually predicted, you know progeria yourself went hand in hand, suggesting that Korea was.
- 00:31:09An inflammatory form of kidney disease that that's what you said rate was up so really remarkable clinical observation so I'm truly honored to be.

- 00:31:18Giving this lecture shipment joining those distinguished names that Dr Cruz, or just the shared on the screen, so I can certainly start.
- 00:31:28Showing on this slide here really well defined the epidemiology is really the burden of acute kidney injury that we face today we'll talk about the major pathways involved in the pathogenesis and discuss some treatment strategies and where some new things are on the horizon.
- 00:31:45want to give you some facts, and this is in light of World Kidney Day, that we celebrated in March.
- 00:31:51Last year, last month, so 850 million people worldwide at kidney disease and just in the United States 37 million Americans and Kinsley so you can just imagine so significant book.
- 00:32:0514% of the United States population kidney disease and, if you look at the impact of that you know it's the eighth leading cause of death.
- 00:32:14hundred and 30 billion of dollars are spent on managing people with kidney disease hundred thousand people start the islands is every year, so that's more than 50%.
- 00:32:25And unfortunately more than 50% of them will die, you know within five years of studying dialysis and unfortunately 90 then don't know that their kidney disease so that's truly it's like a silent killer.
- 00:32:381% of the Medicare population has compete against what 7% the budget Medicaid budget and spell it spent on managing patients with the kidney disease so to look at 33%.
- 00:32:52Of the patients that start Dallas's they live in zip codes were more than 20% of the poverty line, so this is just the port overall of chronic kidney disease, but if you look at.
- 00:33:04acute kidney injury that's a significant component of this burden of kidney disease that we faced on in the United States, but across the world.
- 00:33:13So acute kidney injury was formally you know called acute renal failure and i'll walk you through some historical.
- 00:33:20landmarks that you know got us to where we are with this terminology, so this was first discovered, you know in 1941 we are the London bombings.
- 00:33:31Seeing those horrific images right now in Ukraine with the war with Russia, but it was at this time in 1941 that people were getting carbon the rubble.
- 00:33:42You know, with the crushing injuries and so on, that this gentleman, you know, Dr Eric by waters described in this beautiful paper.
- 00:33:50In the British Medical Journal in 1941 Wayne saw a lot of these people getting caught in the rubble with you know muscle injury that are dying of high potassium levels and the kidneys were really congested.
- 00:34:03And RC as well, so really That was the first description of at that time you know acute renal failure.
- 00:34:09there's been a change in trend in ufology where we're trying to you know, we had chronic renal failure before.
- 00:34:15That we can chronic kidney disease mainly to make it more lemon friendly you know, to the patient patients do you understand Greek or Latin, neither do I, so I think.
- 00:34:25Men fundamental to change we know you know the kidney and failure doesn't sound that great so it was changed to the acute kidney injury and this is just a broad timeline and I showed you 1941.
- 00:34:38Is when this was first described and, subsequently, you know that the various gauging mechanisms put into place, but the most recent classification, is this kp go classification.
- 00:34:49And the definition of a kidney injury, that is shown here on the slide and this really helps when you're doing research are also looking at.
- 00:34:57You know complications in what stage of a KPI are you showing up in the hospital so Stage one is an increasing you're creating all 48 hours by 50 to 99%.
- 00:35:09are dropping urine output less than half a mile per kilo per hour for more than six hours.

- 00:35:14Stage two is anything hundred 299% within seven days and Stage three is more than 200% rise in you're creating your baseline.
- 00:35:25Or you know the before dialysis or you know any other form of regional replacement therapy, so this classification in 2012 2013 has really stood the test of time in terms of research, as well as to some extent management for patients with acute kidney injury.
- 00:35:43You know clearly this disease is on the rise, you know we've got great technology know in an intensive care units.
- 00:35:51You know, brain medications you know ventilators pegboard and so on, so all that has led to more complication that we see in our area with acute kidney injury.
- 00:36:01Unfortunately, the few develop acute kidney injury your length of stay in the hospital increases by three and a half days and, as you know, folks that work on systems.
- 00:36:10Each day in the hospital increases your costs and reduces actually or embarrassment so there's motivation for us to try and get a patient's home quicker, so the shorter your length of stay.
- 00:36:22The charge, you know that the hospital can be cookies much higher so that is a huge issue to increases healthcare utilization for just 5 billion.
- 00:36:31To 24 billion if you haven't completely and God forbid that if you need dialysis that is even higher now almost $11,000 per patient goes to $42,000 per hospitalization if you need dollars in the setting of the injury.
- 00:36:47And the death rate, so this is that way plotted for prostate cancer breast cancer, heart failure, diabetes and if you compare you put all of them together, it still doesn't rise to the mortality that you see with Ak I alone so combined.
- 00:37:04prostate breast heart failure, diabetes and naked eye is significantly higher compared to those and we're still in this pandemic.
- 00:37:15This was as of last night from world leaders, you can see we've been doing this for you know huge waves, you know the delta comic con and so on, and look at the depths so don't even in this pandemic with coven the kidney and significant.
- 00:37:32and actually the kidney after the launch is the second most common organ in law.
- 00:37:38In patients and i'm sure in ufology colleagues have been busy you know doing this time of dumbing.
- 00:37:46down by month.
- 00:37:49With look very early this was during the first surge of the pandemic, you know, a chaotic hospitalized patient with COPD be 19 and what they found was 4000 hospitalized patients.
- 00:37:59About half of them develop aka and have those patients that devout they can either dialysis about half of them ended up dying, you know with a student studying.
- 00:38:14This mount Sinai and subsequently that be a lot more studies from elsewhere, ironically, initially, when we broke out in China, the Chinese.
- 00:38:26issue you know patients that as the pendant expect Europe, France, Italy, in the United States clearly evident that he.
- 00:38:34Was you know, a significant documentation, particularly if you were to go in the hospital recording it and, again, if you had a car in the setting of coke 19 for survival is significantly lower as shown here in the red the red line here so almost you know 40% less survival, if you had.
- 00:38:56The setting of Kobe and again a large you know patient population from five pounds on hospitals in New York.
- 00:39:04And this is just to demonstrate the clinical productivity of nephrology during the first search, this is someone New York hospital again, so the purple line is 2019 admission data, so he ended the yellow line is by default all the hospitals in this job to make the solving it.
- 00:39:27So, clearly, you know hospital admissions drop, you can see you in about 30 40% in this particular hospital but interestingly.

- 00:39:35What they found was the pharmacy consultation, you will be hospital admissions increased significantly, you can see here before number 500 to almost 700.
- 00:39:46Daily you know nephrology cancer patients, you know, during the pandemic.
- 00:39:51And if you look at the number of CRT treatments that was increased almost four five for higher you know, during the pandemic and we face this in our hospital as well.
- 00:40:02Even though our hospital was at 50% volume our consultations were up you know almost three to four form and our rv productivity was extremely high, and you know, obviously fellows and faculty but you know intensively a busy you know, during this time of the pandemic.
- 00:40:21You know, it could kidney injury go live it was thought that you would get injured happy to get better and you would fully recover.
- 00:40:28But now, with the more complex patient that we take care of we're seeing more patients ending up with chronic kidney disease due to that acute kidney injury episode.
- 00:40:38we're seeing more patients that have underlying chronic kidney disease getting aka they get sicker so on, so that.
- 00:40:45significant portion of patients with Ak I end up with end stage renal disease so that's been a huge concern some of these patients with API get discharged and they go to dialysis units were only Asian Canadian girl, and they don't treat them like an incubation and I know very good.
- 00:41:04Dr holly develop special settings where you can take care of these patients at stake here is requiring dialysis and modify that restriction accordingly and not just read them and staging.
- 00:41:17He was telling me about it better than yesterday they don't have the least likely to cover you know, within a few months that they don't mean to be in Dallas, so I think that clearly that sort of focused management of this patient population is absolutely critical.
- 00:41:32And this evening just highlights that fact a few studies, you know, over half a million patients, you know before they had cardiac surgery.
- 00:41:41The GM farm was warning 45 for the hospitalization.
- 00:41:45But if they go naked on most of them would end up you know developing end stage renal disease, they didn't they didn't have a good time to none of that group to develop and still exists, again, highlighting.
- 00:41:57That even when you know better than 45 minutes with this case three he gave people, those can end up with end stage people you actually post.
- 00:42:07Injury setting and the same thing holds true for code that very reason, starting from see on our lead looking at long code.
- 00:42:16So long code of ethics, not only the cart brain in London software can also affect the kittens so shown here in blue.
- 00:42:25is just non hospitalized even non hospitalized patients involve them longer you know, over a year, you can see that has some evidence of kidney moment.
- 00:42:34You know if you're hospitalized that increases significantly I showed you in the green line.
- 00:42:40And then, if you were in the intensive care unit and you had a KPI you have a significant chance of getting you know long Corbett and kidney involvement in the form of you know, chronic kidney disease so very significant.
- 00:42:51You know just not uncommon but we've seen that in the setting of government as well.
- 00:42:57and, more importantly, this is just looking at the hazard ratio, you know if you're not hospitalized the risk of long code with all those two almost three if you're hospitalized without a KPI and if you have a car almost nine fold increase in risk of getting long Coleman from.
- 00:43:16code 90 and again there's a lot of funding that's going to come down the pipe you know, to support long Kobe hopefully this pandemic, you know we will transition to an endemic or some other form once we get you know most recent way.

- 00:43:34Long corporate is probably going to stay for a while and there's a lot of funding coming down and hopefully we can take advantage will learn more about long corporate as well.
- 00:43:44adopt a little bit about sepsis associated with us all of you, you know work that just came in, you know a lot of patients that have sepsis so develop acute kidney injury.
- 00:43:56and not all sepsis associated acute kidney injury is the same, there are differences there are phenotypic differences and a lot of trials have been done in sepsis.
- 00:44:06API and then my work and some reason for that i'll share with you some data from mount Sinai from the original colonies good to have it some artificial intelligence machine learning approaches to see, they can stop classify patients with sepsis acute kidney injury.
- 00:44:26was just using basic electronic medical record data that you would normally enter you know history physical vital signs last resort and so forth just basic nothing additional was done and again large patient population 4000 patients and they applied this.
- 00:44:48algorithm they been able to categorize these patients with sepsis into, for you know phenotype 115 hundred patients to almost 2000 and phenotype three about 660.
- 00:45:01And when they put them in see how well they classified on this plot, you know blue orange and green please this thing, even some phenotypes of sepsis associated at are.
- 00:45:16More importantly, if you looked at complications of these patients, whether they need a dialysis shown here in the Gray bars or did they die.
- 00:45:25You know if you're in phenotype one relatively low risk of dying of eating dallas's versus if you have phenotype three very high likelihood that you will die or the dialysis.
- 00:45:35And this has implications for therapeutic treatments, if you had to do a clinical trials with a wonder drug that you had and you gave it to every patient but sepsis Ha ha.
- 00:45:44You know, it may not work if they weren't, and the reason this if you gave it to something that I wanted may work to get the stuff you know dynamically, it may not work.
- 00:45:54So I think categorizing patients, you know, based on the electronic medical record data that you have and then trying to do a clinical trial is probably the prudent way to go, and these sorts of.
- 00:46:06Sub categorization of acute kidney injury using Ai and machine learning tools, I think, is a huge advantage for us in our colleagues and other specialties cancer and so on, and were had offers in this regard and I think applying those tools.
- 00:46:22You know me too and innovative treatments and some treatments that will actually work, you know patients.
- 00:46:29But i'm a little bit about biomarkers you know there's been a lot of revolution or biomarkers for multiple diseases, including the kidney and This just shows you.
- 00:46:38The nephrons and I promise you, this is probably the only picture and take you back to your university Medical School.
- 00:46:45But just to show us, you know, depending on the area of the kidney that is involved, but as the proximal to build with Marilyn.
- 00:46:52The distal to view the loop of family that are specific biomarkers that can actually tell you, you know, this is where the kidneys damage.
- 00:47:01And this would not have been some nice work by your advisor.
- 00:47:06rush medical Center in Chicago when I found this a biomarker called subpar soluble euro kinase receptor in acute kidney injury So what is this.
- 00:47:16So far, so it's a certainly be informed of a Blocker so far, so good, I had a single anchor to me lovely very low levels, mostly an incremental deals out.
- 00:47:28loans are strongly predictive and progressive decline in things like diabetic kidney disease and so on, so here they looked at a huge for patients.

- 00:47:39With we're undergoing can organic search we looked at the biomarkers and there was a nice twist in editorial this prediction reiki is super important now in a super easy and what they found was they categorize these patients into four different portals and you can see.
- 00:47:59Whether they did on you know match, or they match them or look at multiple variables are single variable didn't match.
- 00:48:07The higher the level of support, you had the odds of getting API after just a simple angiogram which significantly higher compared to you know lower levels, you did not have an acute kidney injury.
- 00:48:20Some other relatively new biomarkers angel points of this work is from colleagues at Hopkins at euro per region colleagues when it looked at the ratio of light on one at.
- 00:48:33Large for one called the SS PT I study and look at almost 750 patients with a out and 17 I did not have it here, and you can see here that not only a few kidney injury ratio was hired correlated with the Bible.
- 00:48:52Worst kidney function but also with heart failure to the blue line is the highest ratio of this angel point in one to two correlated the progressive decline.
- 00:49:03of high functioning as well as kidney function compared to the ones that did not have a.
- 00:49:09Relatively you know well, preserved so there's a lot of research in terms of these biomarkers hopefully we'll be able to use this in the clinic or in the hospital setting to provide an early diagnosis of vacation and so, then we can implement you know the pigments.
- 00:49:26i'm going to go briefly over pathogenesis of aka really not delve into a lot, but really it was important to highlight some of the work in terms of the immune mechanisms.
- 00:49:38Very pioneering seminal work from this division here at uva by Robin Sharma Marco kusa Joel Linden some others that have contributed to understanding of the pathogenesis of API so I feel like.
- 00:49:53Now i'm thinking coals to Newcastle here, but so forgive me highlight some of the work you know from here, as well as other institutions that have provided.
- 00:50:02You know insights for us so very early on, you know, Dr Google that actually showed that.
- 00:50:09You know, if you look at the kidney right after acute kidney injury, this is an animal model, you can see, very quickly, you know this yellow is the neutrophils these are marked by GR one.
- 00:50:21there's a huge increase in neutrophils and there's increases in the cells increases in T cells and then these blue is f4 at these are macrophages know whether the kidney that go up, if you look at the kidney section, the kidney.
- 00:50:39Injury normal so all the macrophage population in the skinny on tagged with the blue and green fluorescent Turkey marker you can see there's an extensive network.
- 00:50:50Of these, green cells within the kidney and you can see a higher magnification that these cells have these extended, you know Ben right like structures, you know within the kidney and expresses protein cx PCR one, so these cells have been.
- 00:51:06The subject of really dense investigation in a kidney injury has been shortened lot of work, but if you deplete the cells before injury do actually decrease injury.
- 00:51:18But if you deplete them after enduring you make injury worse.
- 00:51:22And nobody knew, you know why is this different than the kinetics of the response when you, you know get rid of these macrophages it turns out again.
- 00:51:32that these things are not just one population, you know, like that air for a subpopulation I showed you, but then this thing's been almost seven.
- 00:51:42phenotypes macrophages willing to give me some nice work from.
- 00:51:47July and colleagues for the looked at, you know single cell analysis involved these different suppose you know trump and kidney and how they change following injury is also being studied extensively.
- 00:52:00And what the same group did in a more recent paper was they found a marker for one of the cell population and they call them.

- 00:52:08You know CD 64 expressing macrophage and when depleted this particular cell type offer macrophage it's a subtype.
- 00:52:17In among six or seven different types you actually make injury a lot worse, and this is using cisplatin and you can see the histology as well, much worse injury.
- 00:52:28When you completed the CD 64 collect 19 positive you know cells within the kidney so again, highlighting that you have to get to that cellular level and not just use a you know broad.
- 00:52:43prevent more specific treatment potentially help.
- 00:52:48ameliorate you know disease.
- 00:52:51Go back to you know I told you showed you the slide before acute kidney injury can also you know, lead to chronic kidney disease and what's the mechanistic basis for that again a lot of work has been done.
- 00:53:04And this particular cell type that's been extensively studied is the parasite you know shown here in purple.
- 00:53:11So these parasites are actually supportive cells to the vasculature within the entire body, but it turns out that when you have acute kidney injury these very sides begin to proliferate.
- 00:53:22And there are changes in these parasites with methylation and there are specific, proteins and more than that methylation.
- 00:53:29That, if you have that defective methylation pattern these parasites start multiplying very quickly they become fibroblasts laying down fibrosis extracellular matrix and the kidney ends up with chronic kidney disease.
- 00:53:43And it's interesting that if you can block this methylation pattern, you can actually reverse fibrosis and the setting so we now understand how a.
- 00:53:51single episode of API can end up you know with COPD or even entities can be disease at the mechanistic level in this regard, to a large part of work done by is another highlighting the role of the parasite in the pathogenesis of API at.
- 00:54:10The same thing again was noted bit Coleman there's a lot of debate does stars can be too, in fact, the kidney and a lot of work was done using autopsy samples.
- 00:54:21It turns out it's basically just came out in February in cells stem cell, so this group of investigators looked at.
- 00:54:29Both biopsies as well as autopsy kidneys and actually could find the buyers particle board McCartney as well as protein, you know within the kidney and fossil fuel cells and other cell packs and we've actually isolated urine and isolated itself.
- 00:54:47You know already sequence for source code, we do in the urine results as well, so clearly that it has the ability to in fact.
- 00:54:56In this study, they also stay organized so they prepare to organize these are like you know organs in culture, you take thousand.
- 00:55:04You know, stimulate them with various growth factors and condition media and they become organized like you know, maybe kidneys.
- 00:55:10And they in fact that those organized when the source code, we could find the source code, we wanted one in the kidney.
- 00:55:18And when they block that viral multiplication with the protease inhibitor you can actually use the viral load within these organized so testing again.
- 00:55:28That you know once asked me to give in fact you know the kidney indirectly but, more importantly, they shorten these organized and when you in fact the kidney.
- 00:55:36That down the road they start making enormous amounts of fighting you know proteins like collagen fibers.
- 00:55:44alpha smooth muscle act and so on, so that could be one of the mechanisms of long call with you know he went from single episode of Kobe but you may end up with fibrosis you know within the kidney.

- 00:55:58Some nice work in sepsis is the most common cause of aka is the source work from Indiana university and by pure docker and colleagues but it looked at sepsis in an animal model and what it did within the kidney.
- 00:56:11And the key figure from their studies showing them the slides the label every protein, you know within the kidney and they studied how quickly that protein gets translated.
- 00:56:22And at zero hours, you can see that a lot of proteins, you know bazell translation.
- 00:56:26And and whatnot and for us that increases significantly but 16 hours, you can see that it's very few of these projects, a lot of spaces there so certainly there's a shutdown of this translational mechanism, you know within the kidney sepsis.
- 00:56:41acute kidney injury and they found that one of the key proteins, and that was this elongation factor to alpha.
- 00:56:50And if you block this using a chemical inhibitor called asr IB you can actually reverse substance induced aka.
- 00:56:57So kind understand the medical like you know changes within the kidneys appropriate translation and developing in therapy for a you know, hopefully this will translate to humans and at some point.
- 00:57:11let's talk about you know treatment strategies, what do we have for API, this is a slide that mark accuser shared with me what 10 years ago I'm sorry to say.
- 00:57:21That I still use this slide because it is true, to this day, you know a lot of treatments have been tried in animal models they work great.
- 00:57:30But you do a clinical trial with that it doesn't work and the only FDA approved treatment, we have today for aka is dialysis and we know dialysis is not the treatment for API.
- 00:57:42it's a supportive mechanism to clean up blood and you know, so that the kidneys have time, you know to recover, so this is truly unfortunate that.
- 00:57:51You know this is a state of affairs but there's a lot on the horizon, as I said that before that you know we can anticipate in a way.
- 00:58:00That this is some really seminal work from mark cuckoos of lab using ultrasound alone and, from what I understand this was really a serendipitous finding.
- 00:58:10He was working on setting the scene, you know one receptors the kidney was targeting bubbles and using ultrasound first of all those that.
- 00:58:19You know, cargo would be delivered to the right spot so essentially what he did was localize the kidney delivery possible to sound.
- 00:58:26And then do kidney schema and then look at kidney function and what he found was that when you mentioned kidney function, you know if you do is keep them into a fusion you're creating goes up.
- 00:58:36If you know ultrasound alone, the creating you know the cupboard and if you did this micro bubbles alone, you know, there was no in fact.
- 00:58:45You did micro bubbles and for some, it was a significant protection not only an acute kidney injury, but this figure that was featured on the cover.
- 00:58:54Of the journal of the American society, the prodigy long term, you can see four weeks after mine, the schema that if you have no ultrasound these kidneys look blue that means there's more fibrosis.
- 00:59:07But without to some treatment, who had significantly less by process, so you can look at all these.
- 00:59:12profiles broad in jeans like alpha sm a collagen one college, please my method we're not significantly reduced in the setting, we cannot assign.
- 00:59:23he's done a lot of mechanistic studies to really show that the pathway involved in this involves.
- 00:59:30Learning the College logic system, as well as the Spanish nerves So if you take the spleen out, you can actually lose this effect.
- 00:59:38And the Spanish nerve, which is a branch of the Vegas nerve exactly wall in these anti-inflammatory effects and very recently this elegant paper and pnas from is good.

- 00:59:51Enough stimulation so essentially, just like the ultrasound stimulate the Vegas nerve and then do a schema fusion and cause, you know, look at the animals, and to do that, they developed a really novel animal model were.
- 01:00:04Using a childhood OPS into you can actually like sensitively activate the Vegas nerve by doing laser the biggest target activated if you look at me function.
- 01:00:16In the study and what they found was mentally stimulated this the Vegas nerve after I arrived.
- 01:00:24The kidney function was significantly protected and there's also correlated you know with histology.
- 01:00:29In this in this in the same model so really elegant work and again if you did this Lynette come in the saddle you lost that protection.
- 01:00:37So this could also be easily translatable no way you could use ultrasound activate the Vegas nerve, you know before surgery have a patient high risk to get API cardiac surgery you're.
- 01:00:49Getting a triple A repair or you know getting a high dose contrast when the procedures are transpiring or delayed gratification could you stimulate the Vegas nerve.
- 01:00:59and exploited protected properties to this sympathetic, you know neuro immune certainly it's a very exciting work from marks lab and hoping to look forward to exciting results in future.
- 01:01:14Some other work from other groups, looking at lactate you know we all look at lactate as a bad thing you know highlighted this patient is not to make it or the intensive care unit, you know we always you know.
- 01:01:26really looked down upon the era of the surgeons, you know, giving like data ringer solution to patients but it turns out that lactate actually is protected.
- 01:01:35So this work in a sepsis model where they gave like David riggers when it turns out that lactate is actually protected and reduces you know acute kidney injury in the setting of sepsis aka the muscle look at other models and it is protected, and more recently.
- 01:01:55And this is just the data in terms of bio markers such as Kim one and let you read nitrogen they're both you know reduced following like a treatment.
- 01:02:06And it's done there's a mechanism for how lactate actually protects so this paper and sell from Brian reeves and colleagues actually showed that lactate.
- 01:02:15works through a magnesium channel, you know in mitochondria and regulate cellular metabolism, you know within the mitochondria and the Krebs cycle and that's how like data actually may be listening is protective effects and the senatorial.
- 01:02:32molecular sell or you know all my God, what do you like Dave drives magnesium mobilization so when you give black tape.
- 01:02:39It goes into the mitochondria to these magnesium ions and regulates metabolism, to the citric acid cycle, therefore.
- 01:02:48When you have acute kidney injury giving lactate vigorous may actually be good obviously your monitor you know the potassium so walk but this may be a mechanism for the predicted effects of lactate in the setting of sepsis or you know hypoxic acute kidney injury.
- 01:03:05But talk a little bit about real replacement therapy really answering three questions.
- 01:03:10You know when should you start really replacement therapy you get consulted for a patient in the icu in Europe was going down create things going up, you know, an apologist has gotten salted when do you start dialysis and what's the best modality, should you do seo.
- 01:03:25intermittent dialysis and what's the appropriate those do dollars every day you guys 12 hours a day, six hours a day what's the best modality, but let's try and answer these questions.
- 01:03:38So this is a recent study in the New England journal, where they looked at, you know pining of initiation so let's start early but let's do standard treatment and see what happens.

- 01:03:49So really didn't make a difference whether you live standard or accelerated treatment, it did not matter in terms of outcomes if we started early, it was a higher risk of hypertension and electrolyte you know include chapter.
- 01:04:03But other than that mentality which really is the heart endpoint did not make a difference when you started.
- 01:04:11And this get back to a very old study by Dr Puglia Cleveland clinic you know, on the y axis is survival on the X axis is your critical care score.
- 01:04:21So, if your critical care score is low, you know, whatever modality you use intensive non-intensive your survival is going to be good.
- 01:04:30But if you're critical care score is high, you know whether you use SOFA paci many of them, the higher your score whatever modality use is going to be a bad outcome.
- 01:04:42But it's in the intermediate category of patients, but maybe a higher dose of balances a car, it may actually be preferential compared to less than those or early initiation of dialysis so really this has stood.
- 01:04:55The test of time this is over, you know, two decades ago, but I think in terms of the pillars of balances.
- 01:05:00The individual patient is what you want to look at you just cannot generalize and treat every patient along the same lines, and if you look at the critically ill patient.
- 01:05:09You know, we do continuous respiratory support continuous nutrition, you know neurological status in real support cardiac supports the argument that maybe we need to do, continuous you know hidden replacement therapy as well.
- 01:05:22And, logically, you know you have an intensive care unit with 30 patients requiring dialysis.
- 01:05:27To do intermittent dallas's you cannot have $30 nurses, you know at the bedside you know doing that, so the car, it is usually managed by the critical care nurse so that's more feasible in terms of doing corp.
- 01:05:40And a lot of these bases and a lot of fluid shifts and those are easily better managed to see our team, rather than intermittent haemodialysis.
- 01:05:50A lot of importance that one post hospital API care and the NI to recognize this and had an rfa.
- 01:05:58In 2020 you know caring for our patients after a year is called the call a case study.
- 01:06:05The Pittsburgh is a coordinating Center and there are multiple centers.
- 01:06:09across the country really looking at if these patients Irvine aka in the hospital and get discharged and that population is growing, how should they really be managed.
- 01:06:19I told you about you know performance at it, you know dialysis unit, specifically for.
- 01:06:24Patients, and that is, I think, really important advantage, but these patients really need to be managed as a team, not just a nephrologist but also primary care docs you know the rehab physician mental health issue.
- 01:06:38folks as well as nursing staff rehab you know you need a coordinated team, the family members as well, because a lot of these patients will recover.
- 01:06:47So you need a combined care for these patients that get discharged you know from the hospital after acute kidney injury.
- 01:06:55And a lot of those lines, when mark was the president of the American society and the prodigy.
- 01:07:01He was instrumental in getting this group going called API now so really paving the way to what can we do really impact patients with acute kidney injury, so that, for basic groups here there's a group leveraging basic science to predict Ai there's a group of recognition and management.
- 01:07:21Really, improving education for API you know new paradigms of a care recognition as well, as you know, newer technology what our new pathways we can discover that would enable recovering from acute kidney injury so.

- 01:07:38This has really gotten off the ground, several publications from this group really delighted that mark continues to play a leadership role now it's a lot to come from this group.
- 01:07:50and other really exciting project from the NIH in the kidney precision medicine project or kp empty.
- 01:07:58So the goal of this project is really focused on human can indices to develop individualized treatments and hopefully improve pipeline of young investigators.
- 01:08:08To, why did they really do this study so really, we want a newer treatments for API and seek at night call you a lot of things that we've tried in animal models that not work.
- 01:08:19and clinical trials, then worked it out on the models, but they're not worked in clinical studies so we've got limited availability of human tissue.
- 01:08:29So the goal is to provide a better understanding of human API and SCI fi fantasy to obtain biopsies for patients with Ak and ck the research green biopsies.
- 01:08:41Look at the clinical presentation to do very detailed not only traditional but digital pathology all mix, you know medical omics transcript buildings and proteomics.
- 01:08:53imaging and integrate all that the clinical outcomes and you really create a human kidney tissue atlas and that would provide us with identifying molecular pathways.
- 01:09:04This fact, they could be to being good different drugs and so on, so a lot to look at with this kp MP The great thing about KPMG.
- 01:09:14is really unique is that patients are actually at the Center of this project.
- 01:09:20So yes, there are clinician scientist emphasis, but patients or equitable partners, and they have an active voice in the entire research enterprise.
- 01:09:29So actually the consent form for the Guinea biopsies was developed by patients in this protocol so really you need.
- 01:09:37A study that has you know, hopefully, will do well and address public health problems of the 37 million Americans and I talked to you about the kidney disease and the skinny atlas well you know, I think.
- 01:09:50insights so just to conclude hopefully i've convinced you that API and API transitioning to see katie is a growing threat.
- 01:09:59That are some phenotypes and making that really important to recognize, not all sepsis API is the same, we need better tools, you know.
- 01:10:09Ai or machine learning tools subcategory so a lot of new biomarkers that are coming on early diagnosis of cake Ai and also prognostication.
- 01:10:19lot of mechanisms shortly little bit about resonant macrophages lot of work being done in post hospital care of a cat survivors, and I think it's got a lot of.
- 01:10:29great potential, you know for future developments, so this is just a skyline of Birmingham would love to have y'all come and visit anytime, thank you for your attention and happy to answer any questions.

Unknown Speaker

01:10:51audience questions.

UVA Chiefs

01:11:05start with the one in the chat and then i'll good.

- 01:11:11very nice talk about the right girl.
- 01:11:14I want to go back to the lancome open discussion so you show very nice data that in some cases, the virus can persist for.

- 01:11:23months is it do you think that that's true of all patients the wind covert are some that are the viruses cleared and the real injury continues to the client, despite the appearance of buyers, so I think that's still an open question, but I think.
- 01:11:42it's not probably the persistence of the virus and you know, we had a great talk yesterday about sound the therapeutic interventions that you're doing.
- 01:11:51And there's some work recently that.
- 01:11:55I saw people being treated with the drug you know the Pfizer tax law that yes, initially drop the viral load they'll get better, but once they stop the drug they getting a recurrence of Calvin.
- 01:12:09So obviously not you know Kenny moment per se, but just you know covert symptoms and so on it's hard to tell Joel I'm not.
- 01:12:17100% sure, but we still don't know a lot about this virus, so you know, but I think it's probably an initial.
- 01:12:25response that the virus is causing and that that's triggering some downstream pathways that are getting turned on that leads to long Corbett.
- 01:12:34But it's not the virus, you know, continuing to you know propagate I don't think that's the case but that's you know my guess is as good as your so talk to us today so.
- 01:12:46The question from.
- 01:12:49Can you tell us more about ultrasound treatment not seemingly use frequently I think again, you not feel embarrassed to even answer that question with Dr Cruz, and the audience so maybe, mark you may want to address that.
- 01:13:04i've been bugging into the last few years when are we doing clinical trial on this.
- 01:13:10So thank you for the question regarding office on that yes.
- 01:13:15The effects of ultrasounds in very effective delivering also within the FDA guidelines of using otter sounding.
- 01:13:26And we've shown that in road on and we saw this in the late models as well, and we are now looking to try and use that as an.
- 01:13:41IRB approval for the southern ultrasound treatment so by side here is helping us with us and others are putting this project together to begin establishing when it's been blocked inflammatory response because that's how we think it works, we think that ultrasound stimulates the call.
- 01:14:03So that immune cells in some fashion or not he was exciting.
- 01:14:11Thank you.
- 01:14:25couple pages on the super ratio good prognosticate.
- 01:14:32Do you foresee a world where the regular patient comes into a gas station would actually capitalization guys are constantly here.
- 01:14:42The absolute the people on zoom can hear the question was some of the biomarkers do we see that you know being implemented in clinical care.
- 01:14:52routinely I showed you a lot of the earlier biomarkers which were discovered over 10 years ago, you know and Gail Kim one I'm sure you may have heard of effort check.
- 01:15:01Which is it a BP seven can you know, Tim to some of those are already FDA approved they've not been reimbursed by insurance companies and that's been a challenge on see how we can.
- 01:15:13You know, get that to the bedside I know some of these two are biomarkers.
- 01:15:19Is a lot of work and my gut feeling is start one biomarker that's going to be predicted, you may need to use a panel, you know, maybe three is better than one alone.
- 01:15:29And there's a lot of companies interested in that developing your like a dipstick like a pregnancy test that could be used that.
- 01:15:37You know, you may not have to do, blood tests and so on, and bedside you can you know get the urine very soon within our Sunday June output dropping.

- 01:15:45Today, you get a KPI be better see modeling status, so what drug you're getting to modify the goals and so on, I hope it happens sooner.
- 01:15:55This you know nuances and dumps of who discovered each of these biomarkers They all need to work together.
- 01:16:03So there's a kidney health initiative, not as the American society of the problems you're trying to get these people together we actually had a roadmap, a few years ago.
- 01:16:13You know, looking at biomarkers how how, what can we do to get them to the clinic and I think it's long overdue.
- 01:16:21Because, by the time the creative increases the damage is already done so, we need to you know, diagnose it within hours you know, like doing proponent for Michael infection so absolutely great question, thank you.

Unknown Speaker

01:16:37to your questions.

UVA Chiefs

01:16:44So the question from Rashid the mulligan should every patient that survives aka as an Inpatient be expected to have follow good nephrology afterwards and I, I think, absolutely.

- 01:16:57A lot of these patients think they'll get better and go home but they may not or they'll have other complications of TV or even yesterday, hypertension and so on.
- 01:17:07Given the proportion of patients that have such a high post and I showed you data we call it as well, absolutely I think they should follow up.
- 01:17:16With metrology or, at least if there is no nephrology know depending on where the patient lives, maybe, at least the primary care Doc should have some insights into.
- 01:17:25You know checking the urine to protein checking kidney function and if it's still have normal to refer them, you know to an astrologer side thing absolutely yes.
- 01:17:36And no question from Dr Wolfson.
- 01:17:39That I've been a number of propensity courses for studies showing no significant association between contrast and API implying the association relates to unmeasured.
- 01:17:51confounders is there anything to this so there's a big debate on contrast associated aka versus contrast induced API to really address that and I'd like you to read.
- 01:18:05Recent debate thing it wasn't give me 360 Julie Do you remember that on pro and con you know is contrast API a real entity or not.
- 01:18:17I think, personally, it is.
- 01:18:20You know, having worked with contrast and animals do you have to do other things to contrast to cause a KPI.
- 01:18:27It does have an effect on the vasculature it does have direct toxicity on proximal fuels, it does have direct you know effects and enhancing reactive oxygen species, so it is my gut feeling is you know contrast does cause a KPI.
- 01:18:43But if you have underlying see Katie you have some other cool factors, and those are the patients that you know, makes the.
- 01:18:50environment, you know kind of fertile for getting a KPI that setting so at least I think you know it does cause API, but this is just like you know.

- 01:19:02misinformation campaign with corporate vaccination and so on, so it's not gotten to that level yet, but I think there's a there's a big debate, but I would love for you to read, if you email me i'll send you that debate.
- 01:19:15on that topic there's a pro and con there's a beautiful editorial that that kind of summarize and addicts, the whole thing into perspective so.
- 01:19:26Following the great astrologer to be.
- 01:19:30fluent and he is.
- 01:19:34Fine, and constantly refuted last child, so I appreciate it kind of evidence and physiology that.
- 01:19:42You have a strong opinion on it.
- 01:19:47yeah, I think, by and large crystal Lloyds of preferred aka as long as you don't have you know hypoglycemia and so on, and I think most apologists now have you know gone up Christmas lights.
- 01:19:58And we sat alone, without icu colleagues and across the world, actually to you know discuss that critical piece, there is.
- 01:20:07No fluid overload and intra abdominal hypertension at that goes unrecognized in the patient and the intensive care unit.
- 01:20:15And that's what you just have to be careful with too much fluid where you get you know initial fluid resuscitation is important, but the surgeons would sometimes give you 20 3040 liters of fluid.
- 01:20:26And then you have a you know Michelin man as a patient huge you know, barley mobile lord and it's really hard and that causes aka in and of itself, right through intercom hypertension, I know how often pressures measured, you know, to look for him.
- 01:20:44I think.
- 01:20:46fluids, are important, I think, Chris towards the preferred, firstly in the intensive care unit that's what I would recommend is if there is no, you know, potassium related issues to use lr in a given patient to resuscitate them rather than normal sailing and then.

Unknown Speaker

01:21:03seek or.

UVA Chiefs

01:21:12start a trial and timing and Dallas as.

- 01:21:17A guide I see patients, and I know they look at that a lot of times before in other randomized trials and depending on which file, you will get the findings are different, but it is a bit a bit early Dallas it's not.
- 01:21:29anything to capturing different subtypes of API in the studies or something else you answered your question, you know right there.
- 01:21:38I think it's a patient populations with different in those studies and you're right a lot of New England journal papers lancer papers and on this topic.
- 01:21:47populations have been different in each of those issues with a published, you know the.
- 01:21:52editorials and those editorials really summarize the intricacy of the patient cohorts in those studies, but I think again, it comes down to the phenotype of the patient.
- 01:22:02You know, not all API in the icu is the same So if you sub categorize them then you'll see clear, you know differences in the treatment modality you do so.
- 01:22:13And you know personalized medicine is going to happen right it's already happening in cancer and so on, so this using the emr you know, using machine learning tools to personalize your treatment that's the way you know of the future so for us as well in the quality.

- 01:22:40thanks for that job is complete comprehensive review on the back decoded and you mentioned the viral photos which again evidence that suggests that in Asia.
- 01:22:55yourselves and you also mentioned that there is a transitional making if you see Katie many patients and have a do you think this progression to make it worse, and those missions don't have borrowed.
- 01:23:13Some guys.
- 01:23:19yeah I I don't have any funds done that study in March, but I think he's done the organized data from raw file, you know crime, and I think that's his suggestion that if you effect.
- 01:23:33source code, we do you see the final product proteins that are released down the road, and if you block that the protease inhibitor.
- 01:23:42You know, you lose that you know drop significantly so at least those sorts of legal studies, you know do suggest that that that viral infection, could you know perpetuate chronic immune disease itself, so you know the coven at least would call it so.