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TRANSCRIPT - GR 05 10 24 "***Immunomodulation in Pneumonia Targeting the Host***" Jeffrey Sturek, MD PhD from the University of Virginia

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Internal Medicine Grand Rounds

- Hello! Hello! Hello!
- Welcome to grand rounds.
- Oh, yeah all right. Hello! Everyone. Welcome to Medicine grand rounds. I am excited and honored to introduce our Speaker today. Dr. Jeff. Zurich.
- Dr. Circatina, University of Virginia, for his master's doctorate and medical degree.
- Dr. Sterx, years at Uva, also signed, completing Internal Medicine Residency including a chief resident year before a fellowship in pulmonary critical care medicine which further solidified his expertise in the field.
- Currently, he serves as an assistant program director or sorry assistant professor of Medicine and associate Program Director of Research for the internal medicine program here at Uva, which further exemplifies his dedication to Academia and research.
- Dr. Sturek is known for being an excellent and very calm bedside. Clinician and teacher. Dr. Sturek's contributions to research are vast and impactful, spanning a spectrum of clinical care or critical care. Medicine. Moreover, his commitment to excellence has not gone unnoticed, as evidenced by numerous awards. He has received, both in the realm of research and education.
- His accolades serve as a testament to his dedication to advancing medical knowledge and the next generation of healthcare professionals.
- We are lucky to have him here today to teach us about his work in immunomodulation and acute hypoxic respiratory failure. Please join me in welcoming Dr. Jeff Sterick.
- Thank you. Kara.
- So it's an honor to give grand rounds here for Carrie Marshall Thorner scholars week and it's been a great week hearing about all the work in the division. So in the department. So I wanna talk a little bit about some of the other work that's happening in the department as well related to this topic. But this particular topic's been coming up a lot. Clinically, and so I thought it would be good to sort of tackle some of the evidence and highlight the work that's been going on here, and then the future directions. A a few disclosures that are not particularly specific to this some funding from industry and consulting work. And then we were sites for these studies. And we just got paid to do the work. The only real conflict is that I'm hoping that the last one stays open until the futility analysis. So we can keep enrolling patients but the learning objectives are basically to look a little bit at the basic immunology of the lung's response to acute infection.
- Review some of the latest developments in targeting the host response during infection, and then a little bit of the future directions in host targeted therapies and I think all good grand rounds start with a case. So for this, we have a 72 year old male presenting with shortness of breath cough, and fevers.

- It's been volunteering lately at a local soup kitchen has several sick contacts
- initially, had some sinus congestion and fevers and loss of taste, about a week ago followed about 5 days after, I thought he was improving, fevers had kind of resolved, but then symptoms returned and had new left-sided chest. Pain past medical history is really just notable for some allergies, and hypertension has had a few procedures some family histories of cancers and heart disease is on a blessedly short medalist for medicine. Patient has not smoked. Retired, was a dentist, and no interesting exposures from the hominologist's perspective.
- On exam. He is tachycardic but normal, tensive. He's febrile requiring a couple liters of oxygen, which is not normal breathing a little bit quickly and a little bit of respiratory distress with some crackles on the left his chest X-ray matches your exam and the lambs are really just notable for some Lucas itosis and elevated inflammatory marker.
- So if you are the internal resident going down to see this patient you're gonna be making some decisions right right off the bat, and some of them may have been made for you already. You're probably gonna be wondering about some additional diagnostics.
- You're gonna give this patient antibiotics. Obviously.
- And you're gonna be deciding what empiric microbioles to give?
- How many people in here would be asking, should we give this patient steroids?
- Okay? 1, 2, 3. Okay, some people are asking, should we give this patient steroids?
- And I would say, only in the last few years have we would we have been asking that question at all when I was training the overwhelming question would be even if we're thinking about steroids that we would be saying, Well, I don't want to give them right now, because this patient may have pneumonia, so that conversation has changed a lot, and it's been a fantastic 4 years for this? So I think we are blessed by the opportunity.
- So some things you might be considering. What about the pathogen?
- So what would happen if this Covent patient were Covid. Positive? Right? That's a pretty different decision. But that's only in the last, since obviously the pandemic
- what would you do if the patient were flu positive, would that make a difference?
- What if they ended up? Mercy swab positive! This is something that always gets reported to me on rounds. What's the mercy swab?
- How about host specific factors? So
- maybe this patient is on chemotherapy.
- Maybe this patient has interstitial lung disease, and they're already immunosuppressed at home, and they have a new infiltry.
- Maybe they have HIV and their CD 4 is 0. Right? So all of these things are going to change your approach, of course.
- And then maybe some clinical factors about severity of illness. So what if this patient were not hypoxic?
- What if they were intubated, and so in severe airds.
- What if they were in septic shock?
- All right. So I think a lot of these factors obviously are going to play into how we address the host response to pneumonia.
- But we have to focus here because we don't only have an hour, and so the things we will not cover is antibiotics. I'm explicitly not going to talk about that. So sorry, Amy. You can have Amy tell you all about that another time.

- We are not going to talk about antivirals. So, Patrick, I'm sorry, but you can tell us about antivirals another time.
- And we're not going to talk about opportunistic infections. It's too large of an area.
- But I'm sure Dr. Whistle way, or Dr. Donald, who I saw walk in, would be glad to tell you about that and I pointed out to Jerry, but I am wearing a tie today which I don't normally do. So you're welcome.
- So pneumonia.
- I think it's fun to go over a little bit of history, but to
- to point out that it's a problem. I don't think I have to to sell it to you but 500 million cases worldwide. This is pre-pandemic numbers, a million and a half hospitalizations per year in the Us.
- And ninth leading cause of death, leading cause of death from infection 50,000 per year in the Us. And on a personal note, our friend and colleague, Dr. Shell, recently passed away from complications of pneumonia. So I think we all know that this is real.
- Dr. Shelved. Probably be not happy that I'm not talking about antimicrobials, because I still remember from his teachings on rounds that blur when the lungs are for our our our 4 atypical infection. So but
- I think he would agree that the topic is important for sure.
- But historically, the word pneumonia comes from the Greek pneumon, meaning lung and the descriptions go back to Hippocrates. So a lot of this we don't really know if it's from Hippocrates or from Hippocrates disciples. But I think some of the descriptions are are really pertinent, and they were known for excellent observation, right? Which we, I think, don't do as well today. But here's a description perry pneumonia, sometimes similar a synonym for pneumonia and fluric infections are thus are to be thus observed, if the fever be acute, and if there be pains on either side or in both, and if expiration be attended with pain if cough be present, and the sputa expecturated, be of a blonde or livid color, or otherwise thin, frothy, and florid, or having any other character different from the comment. I think that's a wordy description, but it sounds like a pretty good Hpi for for pneumonia.
- And then when it's bad, when pneumonia is at its height the case is beyond remedy. If he be not purged and it is bad. If he has dyspnea, and the urine is thin and acid, and if sweat comes out about the neck and head, for such sweats are bad as proceeding from the suffocation, rails and violence of the disease which is obtaining the upper hand unless there be copious thick evacuation, evacuation of thick urine, and spew to be concocted, and whether these come on spontaneously that will carry off the disease. So
- This was based around humors right like this, evil humors, which was a prevailing hypothesis about how disease came about for a couple of millennia.
- So you know, they did pretty well with the information that they had as an aside, we're not gonna talk about infayima, but it's pretty cool. What they were doing, apparently they would sometimes intervene surgically on plural space infections.
- And this is a description. The sharp knife surgical knife is to be inserted between the ribs adept equal to the thumbs.
- Nail length towards the Npm. Is area. With the help of a knife.
- A linen cloth is inserted, sewed locally, and used as a spy, which is like a spigot to both attract the pus and block the air. The linen door is to be opened daily for the pus to be drained, or or at least 10 days, with the help of a catheter.

- An area is clean and the fluid is similar to water. Antiseptics are to be infused a mixture of olive oil and wine and left there for 12 h.
- The synthesis of the surgical wound!
- Yadda! Yadda! Yadda! So that's pretty cool, and this is some images of believe it or not. These
- The lower left knives are from Uva collection, actually. So we could wander out down after it and see what they were using.
- And I think that this mixture of olive oil and wine is, I mean vinaigrette in the chest. I wouldn't have figured but this may be the first Tp Dns so we do something a little different today. But it's pretty impressive what they were doing.
- So let's just review a little bit about the normal host response to infection.
- It all sort of starts with airway anatomy. So just to remind you, there are
- 23 ish divisions of the airway from the tracheon down to the Lvl. I and which looks like this, and it provides a lot of opportunity to capture microbes on their way down to the Lblis, where they would cause pneumonia and obviously a lot of surface area for gas exchange and the anatomy is different. Whether you're in the airway or in the Gas exchange portion in the airway as pertains to as pertains to host offense. It's really about Mugo celery clearance, right? So we have this mucus, mucosillary elevator which catches bacteria and other inhalational microbes to carry them to the mouth to be expectorated. There's lots of components of mucus that are involved in sensing what's in the airway and determining whether it's abnormal or not, and coordinating a host response. And it's a beautiful picture of me and production. And that includes sort of obviously various enzymes antibodies, things can continuously sensing the environment.
- Once you end up at the Lvl list, then we're talking about surfactant which is there to facilitate gas exchange. But there are also surfactant proteins which help modulate the host. Response. They enhance.
- Figure. So figure cytosis of of bacteria that may get down to that end of the airway, and they can inhibit growth of pathogens as well.
- And, as you know, Surfactant is continually being recycled, and Lvl macrophages are one of the resident host cells that are really driving a lot of this coordinated effort. I'd like to thank dr. Carlson for setting up all of this beautifully last week, only he talked about the evolving room escape, because that review of immunology was great, and one of it was through signaling, through pattern recognition recept receptors which since foreign patterns on bacteria and viruses through lots of different receptors toll like receptor receptors, scavenger receptors and lectin receptors and a lot of these are being done by these resident professional antigen presenting cells so resident macrophages, patrolling monocytes and dendritic cells. They're all sitting in the airway at different levels, sensing what is in our environment and poised ready to recruit the professional immune cells to clear the infection.
- But there are also nonprofessional antigen presenting cells. So all of the cells of the airway epithelium as well, will have lots of these similar receptors and to similar degree, are able to sense what is happening in in the environment and recruit the immune system to a side of injury and a key takeaway is that the neutrophils in a lot of cases are the first wave right? So these come in when we have a cute bacterial infection release a lot of enzymes and extracellular traps, and cause a lot of local damage. But take out the infectious agents along the way.

- And then the adaptive immune system is ever growing and complex, and a simplified version of the T-cell immunity on this side is CD, 4 T-cells with these different arms, which you are probably used to hearing about.
- The one primarily for intracellular and viral viral clearance, and th 17 primarily for extracellular, bacterial, and fungal clearance and the various cytokines that we associate with drivers of these types of immunity.
- Cda T cells being the side of toxic T cells which come along to kill infected host cells and then, the other side being B cell immunity which is primarily directed towards antibody production at sites of infection.
- And there are natural antibodies which come about that do not have to have seen infection for them to be present. But the vast majority, when we're talking about infection, we're talking about adaptive immunity and and memory. For when you see that infection again so how we suppress the immune response to infection starts with glucocorticoids, and it is just and ridiculously large topic, and impossible to dive into all the mechanisms of gluicoroids. But I do want to just highlight, some of them that will be relevant to the talk which is they inhibit. Leuco trafficking to many sides of inflammation specifically for monosites and macrophages, reducing production of a variety of pro-inflammatory mediators neutrophils. They, as you guys know, when you get a Cbc on a patient who ha is on steroids, they increase release from the bone marrow, and they also inhibit apoptosis. So while they inhibit migration to sites of infection, they do prevent apoptosis, so they will hang around a little longer.
- Generally you get a T-cell lymphopenia. And they obliterate Esmfils. Basically. So if you have es and affiliates on steroids, that's very abnormal there are clearly many, many chronic effects of steroids, which is what is very well documented, that they increase the risk for a variety of infections which we're not gonna talk about today. But we're gonna focus on their use acutely in the setting of acute infection.
- And this is just a a slide from a now very old review. That shows that this is really the slide hammer. If you want to by and large reduce nearly every aspect of the immune system. You can slam someone with glucocorticize as a first pass.
- It comes up with dosing a lot, so I want to mention it. But I want. I don't want to dive into it too much, but you all are probably well aware.
- All of the glucocortic codes have various different activity levels and there. Different doses will be used in the different trials that we're gonna talk about. I like to say on rounds this mnemonic don't stop, Fred hastily. 1, 4, 5, 20. So if you are trying to figure out the equivalent glucocorticoid dose for your patients, you can use that or go to one of these tables.
- So steroids in community acquired pneumonia. So they were proposed as early as the 1950 s. Actually, there have been multiple, small or retrospective studies suggesting benefit.
- And we have a few lessons from Airds as well, which I would like to talk about.
- So this is a paper from 1 55, actually, where they propose to use steroids in pneumonia and they specifically focused on pneumococcal pneumonia.
- It's an interesting read. You have to, as you can see you have to get it by in our library alone, because they're photocupping it out of the actual book.
- And this is a description of the therapy, which is basically I am Penge every 12 h for 7 days, or until they're a February for 48 it doesn't seem like there was consent in this study because it wasn't described. And it was just everybody that came to the hospital.

- And it was the the randomization was by your number. So if you had an odd number, you got one treatment. If you had an even number, you got the other one and they focused on clinical presentation and symptoms. And this is just an example of, like one of the pieces of data that they have in the study which is showing the fever curve on and off hydrocorps. So they got hydrocortosone and you can see that they like Defra vest on hydrocorton. And then the fever came back when they stopped the hydrocorticone. And so all of the this is a relatively small study, but it was all the data was sort of for improvement, earlier improvement and fever and symptoms was, was sort of the outcomes from this study, and they obviously were not powered for mortality.
- We didn't have a lot that changed the landscape, but it was thought of early, which I think is was an interesting thing to bring up but a lot of our practice pattern, for I would say the early aughts to to the pandemic was based on data from Airds and the landmark study in Airds was a Lazarus trial, which was a late administration. So in that study patients who had established airds were randomized to methylpred and that it was they had to be from day 7 to day 28 of Airds. So they were past their initial acute phase and the hypothesis with that was that sarids would sort of that they were. You're not going to affect the initial and anti-infection immune response. But maybe you could promote recovery.
- And it did not improve 60 day mortality. There was a slight improvement and bent later free and Icu free days, which is, we generally use pretty routinely now. But importantly, if you were randomized after 14 days of Rds. That was higher mortality compared to steroids. So these are the largely overlapping survival curves. And then the mortality broken down by early Ish. Versus late, which suggested the steroids were bad. So of one of the many negative Rds trials. This one is the one that kind of made us say, well, we probably shouldn't be clearly using pneumonia steroids. In this case, I would say, point out, by the way, a lot of these patients had pneumonia, so I think it's it's apt to apply to this disease but there were a number of studies, and then in in 2020 this was published. It kind of got overshadowed by the pandemic, but a in another steroids, airds. Trial was done, and this one was for earlier steroids and irds moderate to severeity. Yes, and what they did was they waited 24 h until, and if you met once you've got diagnosed for it with Rds. Wait 24 h to make sure that you didn't recover very quickly, and then you got randomized to steroids, and this one was dexamethasone, and it was stopped early, due to low enrollment before the pandemic, which is
- Just interesting timing. I think they would have made it if they had waited a little longer. But you know the outcome was ventilator 3 days at 28, and it was, you know, significantly better, as was all of cause mortality at day 60.
- And so in cases of severe ards, in which case, again, most of number, I think about half the patients in the study had pneumonia. You know, we're pretty liberated from this to say that steroids can be beneficial and then there have been a number of studies, smaller studies with endpoints that sort of non mortality based endpoints that suggested that that steroids would be helpful in pneumonia. And so one of these, was in Jama in 2,015, and they looked specifically at patients with severe pneumonia with a high inflammatory response based on crp. So this is a multi-site trial crp greater than 150, which on our units of measure, would be 15.
- Yeah, you look at 100. You're like, I've never seen that. That's why. And they got half a Meg per kig of methyl bread.

- And the primary outcome in this case was treatment failure, which is a very complicated outcome. And it's like I can't put the whole thing on the slide. But basically composite of getting worse early or staying bad later is how I would summarize that outcome.
- And it was a relatively small study, and it didn't move the needle much, because it was basically a somewhat small effect. Size on, you know less treatment. Failure with steroids but 2015, I think, didn't really move the needle much.
- And then in the same year, there was a much larger study, looking at prednisone with community card pneumonia.
- In this case they did not. So, you know, there was no, and inclusion criteria for, and inflammatory markers, and it was Pred 50 for 7 days. Very large study and this endpoint was timed to clinical stability. So it's another one of those endpoints that's like harder to hang your hat on the more than mortality. But basically, do you look better earlier? Pretty similar to the 1955 study and that showed improvement with prednisone. So these are the probability Kaplomar curves. And then just focusing in. There were increased complications, which is something we're obviously always worried such to some degree about the hyperglycemia. So there was an increase unsurprisingly in hyperglycemia, in the, in the steroid treated groups, but they still, you know did got better earlier in this study and I come back to that study later for some other data and then everyone got unenthused, because in 2022, the one that was powered for mortality was done, which is the escape study.
- And so this was another large study, and these are all icu patients with severe cap and they got methyl pred for 7 days and tapering over 20, and the outcome was all 60 day, all cause mortality, and and they were just very not exciting, overlapping survival curves.
- But simultaneously this Cape Cod trial is happening which landed in the New England Journal in 2023, which was a similarly designed study, admitted to the Icu for severe cap and they got hydrocort for a similar duration and the primary outcome was death at 28 days and in this one they don't overlap, and you have a benefit if you, for survival discharge from the Icu in this case is what's represented for hydrocor and it's a pretty large primary out, I mean, if you look at the primary outcome of death by 28 days, we're talking about 6% versus 12%, which is a pretty decent effect size for this disease.
- So why are these studies different? This, I think, is kind of the crux of the issue of how do we? How is our practice pattern going to change with regard to steroids in community-acquired pneumonia?
- And there are a few differences between these studies that people are trying to sort out. What what is A driver here? So for the Cape Cod study the positive study. They were randomized within 24 h of diagnosis of severe commute quite pneumonia with escape. They allowed this enrollment window out to 96 h. Okay?
- These are relatively sterodosing is essentially equivalent and the duration is largely equivalent as well, although a little more flexible. In Cape Cod.
- The escape study was done through the Va. So this is a large, is like almost entirely male study and there are some subsequent analyses that suggest that there may be a sex dependent effect. We don't really understand the mechanism of that, and it was still a predominantly mail. Study the the Cape cod one. But that is something that people are interested in.
- Importantly, as I'll touch on later. Cape Cod excluded influenza because of prior data that suggested it would be harmful. Escape did include them. There were only

18 patients. So it's hard to see that that really drove the outcome. But there, that is a difference.

- And then on biomarkers most of the Cape Cod patients were pretty acutely inflamed, based on Crp that there is, as far as I can tell. There's an ongoing analysis with escape that I don't think has been published yet but they obviously have all the bios specimen that I'm sure they're gonna be cranking through for years.
- So I think, for now, on regular communicate pneumonia, you might say the jury is out, but the bulk of the evidence, I would say, leans toward giving steroids in the acute phase, and we'll get to that in a little bit later. But let's look on a pathogen specific level at Covid, because this you all probably know very well, but
- I think, really changed our view of how to handle acute respiratory infections so we're gonna talk about dexamethasone. We're gonna talk about anti aisle, 6 therapies. And we're gonna talk about Jack inhibitors.
- So as you guys probably remember the Recovery group trial improved mortality, but it was limited to those who required supplemental oxygen and was most effective in those who were mechanically ventilated.
- I would say, this is like the fastest adopted clinical practice change that I can remember in my short time, because we were essentially acting on preprints. But these are the survival curves, and the the key thing to take away is that in the all in the no oxygen which is in the lower right. They were essentially overlapping. And actually it was like towards harm in the Dex method in the Dexa Method Zone group, which is why, our practice pattern changed to basically treating every hypoxic patient with coat that had covid with steroids. And I'll just point out the numbers here. I mean, this is a study with
- 2,000 patients in one arm and 4,000 patients in the other arm. So part of the reason this has been exciting for years is because we have been able to have very quick gratification on our clinical trials, designs, and outcomes. You would never, I know cardiology has big trials, but even even for cardiology standards is a big study an anti aisle, 6 therapy.
- We have recovery and remap cap, which were the leaders. Here, in summary, it was improved survival probably, in those patients with elevated inflammatory marker and crp of 7 and a half as our cutoff for for this key exclusions for these studies is that they excluded clear clearly other infections, so would not apply to our all comers, Cap. And if you had elevated lfts and that this is just a survival curves from those groups which is basically showing you what I just said.
- The Jack inhibitors bear set nib tofacet nib act 2. There was the outcome was time to recovery, so that was in in hospitalized patients. Importantly, Dexamethone was not included in that study. And then Cov barrier, which was a survival benefit. But this was limited to patients not on mechanical ventilation. And they had to have at least one inflammatory marker. Other important exclusions, which you all probably know from prescribing. This is the you have to monitor for lymphopenia and renal failure was excluded, as well as other infections and those are the survival curves that essentially say that which are not projecting very well.
- Other studies in Covid that are host directed have largely been not very exciting. The interferon Beta study with Act 3 showed no effect, or worse.
- Remember hydroxychloroquine. Well, all people remember it well, no studies of very bright light or bleach. Thankfully. Active 4. Which was all this Rast targeted stuff.

- Was kind of an interesting trial. There were 2 drugs in the Ras system under nectar, which were both terminated early and are published. There was no benefit. Needless to say there is one under analysis, which is foster matin and foster matin of, is a pretty interesting drug. It's used in Emon literature, and it inhibits it targets. This concept called Thrombo inflammation, which is the idea that there's increased thrombos, thrombosis in cute sars going to infection, and that this inhibits this extracellular trap net formation. So there's a lot of excitement about Foster, and the manuscript is under preparation for publication now, so I'm sorry I'm not. I don't think I'm at liberty to disclose the results of the study, but they will come out soon.
- And then Panama, which I think is for Villabella map, which is monoclonal against C. 5 a, which is terminal complement. Again, a lot of compliment, activation and acute infection actually, it was an interesting study that did show some benefit and severely ill patients. I think it is not likely to be adopted universally. We looked at bringing it here, but basically we decided not to, because under the current state of rate of severely ill COVID-19 patients that would fit into the inclusion for this, we basically just didn't have the patient population that it would benefit, but they are still, you know it. It's available. And it got recent Eua for critically ill patients. So targeting the complement cascade certainly may be appropriate in some cases which is interesting.
- so there's been a lot in Covid.
- There has not been a lot in influenza, and I want to go through a little bit of that literature now and so all of the data and people have been steering clear of giving stories explicitly and influenza there are virtually no randomized control trials. There is observational evidence for harm which we're gonna look at.
- And so this is from a very large, nice Cochrane Review in 2,019, where they looked at a bunch of studies, as they often as these are designed to do. All of these, with the exception of one study, are retrospective studies, and whether they do an adjusted mortality or unadjusted mortality, you can see that the odds ratios favor no corticosteroid in influenza infection.
- Similarly, the when they look at acquired hospital acquired infections as a potential mechanism. For why this might be again, it favors no corticosteroid, meaning that patients who got steroids when they had influenza tended to get more hospital acquired infections. So it seems at least based on the retrospective data that for acute influenza it's not the same as acute covid, at least, so the data would suggest. And that it's not really helping the initial response to influenza.
- This is the data that we have, which is from that 2,015 paper where they looked at prednisone in community, part pneumonia. They looked at pre-specified subgroups based on the pathogen. And they we're and based on antibiotics and and pro calciton, which I'm not going to get into. But the bottom line is that on the pathogen side there was no difference on any of these subgroup analyses, saying what pathogen is driving it so steroids for community acquired pneumonia in this study you know, there was no effect breaking it down by pathogen, but I would point out that the influenza virus there were 11 in one group and 13 in the other. So clearly, we're not powered to answer any questions here so why is this? And I asked gee this question because I was wondering it as well. And there are a few things that are maybe different about Covid and influenza. So one of them is severity of illness, generally speaking, especially pandemic covid, I mean the rates of severe illness from that were clearly much higher right? There may also be something about timing here, so generally speaking, and one of the things that made the pandemic

hard was that there's a pretty significant delay from your exposure to symptom onset, and then to severe illness, which gave us a large window of opportunity to intervene on the immune response to infection. But with influenza, as you guys probably know, anecdotally.

- It's a pretty narrow window of therapeutic opportunity. Let's just take antivirals, for example, you have to get the osultam of beer in early, or it generally doesn't have an effect. It's probably the same for targeting the host and then there may be virus specific factors on a mechanistic level.
- But they the more studies that are done I feel there's probably more commonalities than differences on some of the immune response.
- But I think it has to do with what's been done so far. So here, that's this what I figure I just showed you showing there's 11 versus 13. In the in that randomized study the only other one that is available is from the not Cape Cod trial. The the negative study from 2022 and they did break it down for influenza. And this is they only tested for Lorenza and influenza in about 60 patients in each group. And only about, you know, 10 or 8. So we have like very significant lack of data in acute influenza.
- And compare that just to recover. For example, I already said, 2,000 4,000 patients. We just haven't had studies that are powered to answer this question for influenza but I think the studies are coming. So we decided not to bring it up. But there is a study that I think is awaiting funding where there is a 2 by 2 factorial design that's testing early initiation of antivirals and initiation of steroids and acute influences. So I think we will eventually answer this question, but it may be harder to do without an influenza pandemic, which I'm not asking for, just saying that it would be a lot easier if we had a pandemic so future and ongoing studies very excited about this platform called Strive. So during the pandemic, when the nih was trying to execute all of these studies and bring them up very quickly. What they did was use existing trial infrastructure for other studies. So people that were doing studies of valves for cardiac disease ended up doing covid studies.
- Well, all those folks are back to doing their usual thing now, and Strive was born out of that. And it is using that existing clinical trials infrastructure to keep it in place for fingers crossed the next pandemic or also looking at other infections. So we're focused on, you know, better treatments for severe respiratory infections and maintaining this infrastructure. The for now the focus is on hospitalized patients with severe respiratory infection. But there may. This scope may creep and I think we will, for now the focus is still on Sars Cov. 2. But I think influenza will undoubtedly be involved. So the first strive trial is an antiviral which Patrick Jackson is leading from our group. This joint emerging diseases initiative, Jedi, which Kyle named when Patrick Kyle and I started this in the pandemic have brought up a number of these trials, and so patrick's leading this one on this protease inhibitor and then the second trial we did not bring up yet. But it is really honing in on when to augment immunosuppression in Sars Cov 2 infection. So basically, it's a complicated inclusion criterion. But if someone is on escalating levels of oxygen requirement, but hasn't quite met the requirement to get to see or Barry and so it's really it is very baby bear study, which is why we didn't feel we had this patience for. But I think it'll be interesting to look at early versus what I'm calling conventional dual immunisation it is using this drug called about asept, which is a coastal military blocker.

- Truthfully. That's because that's the company that wanted to be involved in the study. And that's just kind of how it goes sometimes.
- But we do have one open here, called tilia, which is targeted at aisle 33 aisle 33 is in this category of alarming.
- this is an overly broad schematic of what aisle 33 can do. But it's basically released by damage epithelium and can drive lots of different aspects of the immune response.
- And so Astrazeneca has a antibody targeting aisle 33. And so this is a study uses that anti aisle 33 for respiratory viral infection. It's for hospitalized patients who are hypoxemic, and they have confirmed or suspected respiratory viral infection. So they really want us to get this drug into the patients early. It's within 36 h. And so you don't even have to be viral swab positive. If everything looks like respiratory viral infection, and you're waiting on the you know the broad panel, your quad screen negative. You're still eligible for this study.
- And the primary endpoint is death or Ecmos at 28. So it's gonna be, I think, interesting. We'll see. I think we're approaching interim analysis now.
- And I just wanted to highlight that since it's a DM. Scholars week, some of the ongoing work here at Uva in this space, and a lot of it is around, not necessarily just intervening on acute infection. But how do we understand people's recovery to infection?
- Because mortality is clearly an important endpoint, but when we try to understand. How are we taking care of our patients? It's not just do we get them out of the hospital alive. But how do they do afterwards, and the repair of the lung as people recover for infection. And so my colleague, G. Son, who's been doing a a wide range of excellent work on the basic mechanisms of Sars. Cov. 2, and influenza with other papers coming out now is working on these things. I'll point you. Towards one of his many papers Bill and Jen led the phase, 2 study of Dupont targeting type, 2 immunity in Sars infection, and are working on subsequent studies, and it really partly focusing on that patient's recovery from that to in their lung function. And Judith woodfolk and allergy is really focused on the
- T cell signatures in recovery from Covid.
- Our own Kathy bottom. Kathy, I love this picture. She clearly doesn't. But I don't know what this article is from, but it's like you're very pensive in this in this one. Looking at how understanding how people's immune systems recover from Covid, and how that looks like ipf
- you can give me a better picture later, Kathy, for the next talk, and then in the post, Covid clinic we are bringing up these recover trials, which are multi-site trials in long covid, as tarting all aspects of of recovery, including the immune system, and Alex is leading those so with we're actually doing really well on time, to my surprise, so I would like to summarize by saying that
- I think steroids are beneficial for hospitalized patients with mean acquired pneumonia. As far as I can tell, the Idsa guidelines have not reflected this yet, but I would not be surprised if the next edition says that we should use them particularly early in the course of the disease, because that's the biggest difference in timing, in my view, between the largest studies in that
- It's obvious that it is the case in Covid, and that they probably also do better with additional immunosuppression, and the timing is up for grabs there.
- There are lots of ongoing studies testing inhibitors of specific immune pathways and acute respiratory infection as well as recovery and antibiotics are important, too.

But this is a really beautiful review of the viral response to infection from G's group. And I don't have time to go into all these mechanisms. But I just wanted to point out this really cool graphic of the Cytokine storm.

- Which I think is what we're talking about here. So Cytokine Storm is really part of what we're talking about, right? That it's partly your sur. The survival from respiratory infection is not just about treatment of the infection, but about modulating the host's response to that right. This is why people accept it. And
- I think that this is the modern version of evil humors. Because what we're really doing is targeting the response to infection and trying to return balance to the system.
- And I think we're gonna learn a lot about how we do this in the coming years. So that is all that I have for today. I didn't go through a lot of the other work that these people on the slide are involved in. But I wanna thank all my many collaborators here and be happy to take any questionsnfor anyone on Zoom. Please feel free to pop some questions in the chat. Otherwise, if people have questions, I'll pass you a microphone. Oh, wonderful!
- That was! That's great! Jeff. The different steroids. You showed data with dexamethasone. There's some data with hydro portisone. There's the happy solid in between of those. What is your preferred steroid for a patient? Not non Covid, or with Covid as well. Yeah, I I mean, I think, for now the bulk of the evidence would either be for hydrocor or decks if they're not critically ill and their usual hypoxemia from Covid, then they get Dex and meth zone, because that's what the bulk of the data is from if they have developed septic, I basically the the short answer is, I look for the other indications. If they've developed septic shock, then hydrocortons, probably the right choice but from a glucocorticoid perspective. I'm not aware of a good reason mechanically to use one or the other apart from maybe, like hepatic conversion of oral prednisone. But I think you have the license to use any of them.
- If that is a reasonable thank you. I can hear. I enjoyed your talk, you know, brought back some memories as well. So I was trying to figure out, you know, when you see these very sick patients. I mean, can you tell whether the patient is very ill because there are too many pathogens in his body versus whether this is damage from a very exuberant inflammatory response? Are there ways that we know of that can? Because if you put the subset of patients where there are too many pathogens on premise zone, then you might be doing some harm while if the patient is very sick, because of an very severe informative response in, and it will help.
- So from your studies. It looks as though, when someone is sick you either put them on premise owners or not, and whether we can do a better job.
- Better defining those patients first before putting them randomizing them. Yeah, that's a good question. I mean, I'll just give the example of aspiration pneumonitis, right? So I think resonance rounding the icu know the aspiration pneumonitis and pneumonia look basically. Exactly the same clinically in the first 24 h.
- Aspiration pneumonitis gets better, faster. Pneumonia doesn't. And so but your question is, how do we say in the beginning, apart from the clinical history, what's the what's the indication? How do we know who to treat and who not to for now the best thing that we have is, you know, pretty non specific inflammatory markers like Crp for respiratory infection. And then your point about the sort of subsequent.
- either secondary infections or control of a of a poly microbial infection, I think, will ultimately probably have to do with the duration of our steroids, because in the short term I think you're probably unlikely to make a severe infection worse. But as

we were, as you get to the phase, the sort of more to the recovery phase of illness is probably where we need to be smarter about getting steroids off and allowing the adaptive, immune response to, you know, supervene. So I don't have a good answer, and I'm not aware of any current studies looking at better biomarkers of early pneumonia to decide who gets steroids or not.

- There will undoubtedly be follow up from some of these larger studies that were just published in the last year. So it may be that those will come.
- So we'll see. I sort of a follow up question on that. You talked a lot about by pathogens did not too much dividing it by patients. We talked about hospitalizers versus non hospitalized hypoxic non hypoxic. But are you noticing any trends in the data towards certain patient populations. Maybe like, are these smokers who have undiagnosed C. Opd, or these patients with other atopic conditions? Is it just, you know, a heterogeneous group? And some of these patients would benefit.
- Yeah, that's a really good question. So for a a lot of the more pragmatic early Covid studies, there were not as many exclusion criteria. And so I think they're probably more generalizable findings for the vast majority of the more recent studies and the currently ones we have ongoing. They exclude a lot of the conditions that you're asking about. So clinical trials designed for these studies typically excludes patients who are like immunosuppressed for transplant, for example, or who are very cytokic. And so unfortunately, we just don't have, as far as I'm aware, for regular or community pneumonia. We don't have good data about immuno modulation in those special populations. But I think the way that I would apply the data is that historically, we would be afraid to give steroids if we thought that that acute respiratory infection was driving severe illness for the other indications. Whatever those were, I don't think we should be afraid anymore. Right like, give your C Obd patient the prednisone that they need. Give your, you know. Multi presser septic shock patient, the hydrocor. Does that make sense.
- So have you? You know other studies where people have looked at different cytokine levels in the serum, especially during the covid infection, and found a correlation between those who respond to steroids versus not, you know, based on, say, if someone's making a lot of higher 10, do they do better or something. Yeah, that's a really good question. I don't know. There may be someone in the room who knows? I'm not sure. And are there any mouse models that they have been done this work on? Yeah. So so the first question, are there serum biomarkers that can stratify responders and non responders for steroids? I'm not aware of any, but as with any covid literature, it may have come out yesterday, so there may, if someone in the crowd knows, please comment. But I am not aware of any that that helps stratify. There are, of course, unlimited number studies with looking at Serum Cytokine levels.
- And then the second question for mouse models. Yes, there are mouse models of Covid and and Bill and G both work with these a lot.
- Basically 2 flavors. One is in the k teen transgenic which is, you know, over expressing human ace, 2 receptor, and then in mouse adapted strains and they both have their limitations you know I don't, really. There have been many studies looking at other modulators of of inflammation which are, we're on some of the slides that I showed. But I'm not aware that they tested steroids. I'm sure some have looked at Luke recorded place, but I'm not aware of it.
- Patrick may have had his hand up. Great. I actually have 2 questions for you, and and one kind of pertains to the how we're organizing trials. And this kind of goes to

Dr. Logo's question why did we not look at Cytokine levels in Cape Cod? And why do we not have these answers?

- Yeah, I mean in Cape Cod. So there was a look at Crp but yeah, no like. It's not part of our current practice, anyways. And the but and they explicitly in the other study.
- It says we have, you know, samples, and it's ongoing analysis. I just haven't seen it. Land, so it may have landed, and I missed.
- But I think yeah, to your point. There, there we have to be better about stratifying, you know, who's going to benefit and who's not so far, clinically. There, there's not a lot in within those trials that really is able to discriminate what's that? And I think you know, speaking as a clinician, a researcher, too. I think it also means that we should be demanding more from our research trials. And if we're gonna talk about translational research. It's kind of a no brainer to incorporate some of this that said, we don't know. It's not published so
- I think it's a question we would like to know, and I think it'd be helpful in these trials. The second thing is and I might be using this
- to to to to have you do my let search for me. But if I recall the other aspect of Cape Cod and the other trial, was it? I think it liberated us from being concerned about the use of steroids. So our concerns about super infection, poor blood test, control and wound you like that. All went out the window with those trials which I think also gets buried and I think that's also worthwhile. Now, it doesn't seem to really be harmful and I think delirium as well doesn't seem to be harmful to our patients to be using steroids in these circumstances. And I think that's important to say aloud, too. I completely agree. I mean, I think that's part of the the message. Is the conversation as we tectonically shift our practice. The conversation used to be. I'm worried to give steroids, because I think they have infection, and I don't think that should be the conversation, you know it should be.
- Are we giving it early enough.
- Can we get it off relatively quickly? You know that that the nuance will be in the timing. But yeah, I think it should relieve the fear.
- Since I have the microphone, I think I disagree with that a little bit, because the recovery trial, the recovery trial right. You saw a trend towards harm in covid patients who did not require supplemental oxygen and got steroids. And I think one thing that gave me a lot of heartburn during the pandemic was you know, if you're a patient on 2 leaders on the floor, are you more like the oxygen requiring patients that derive mortality benefit? Or are you more like the patients who didn't require oxygen, who might have had harm. Because, as you mentioned, this is a pragmatic trial. We don't really have any biomarkers. We're just kind of like guessing what Uk clinicians think is sick enough to acquire oxygen. Right, which may be different than our than our judgment of that, and also the experience in India with using large doses of steroids.
- In COVID-19 you saw a lot of invasive fungal infections, a lot of invasive mucore as well. So there certainly is. I mean, you can obviously say they were just misusing and using an appropriate doses, which I think is probably true and also different epidemiology of invasive fungal disease.
- But certainly I don't know that it gives me a whole lot of reassurance. I think I still feel anxiety about steroid use in covid and and in other respiratory infections. But kinda to that point, actually, you know, you kind of mentioned the that that crp is kind of a useful marker if you're designing, you know this trial. Looking at interventions to modify the host. Immune system. What markers do you think are

useful from a research context that might actually have application in the clinic? I mean, you can immunophen type people all day long in the lab, but like things that would be kind of of practical utility down the line. Yeah, no, it's a great point. So thank you. To my colleague and co-investigator and id physician. Patrick, always available for a good argument, and and I so I I take your point, and I think it is very clear that has to be the right patient.

- And so the data that I could then also point to would be the specific inclusion criteria for Cape Cod.
- As pertains to the clinical presentationnand that is for Icu patients. Or and I think Icu is a is a dumb inclusion criterion, right? Because it's about as useful as whether Uk clinicians feel that they need oxygen to your point.
- Nothing against the Uk. But as all residents know whether someone gets the icu is not a particularly objective thing, but they did have psi score in there as an inclusion criterion which is a relatively well validated objective measure, and psi scores 130, was the inclusion criterion for the study. So if we go back to my case and do a psi for that patient.
- We could make the decision that way. So I'll ask the group for my 72 year old on 2 leaders breathing 24 times a minute.
- Are. Who's going to give steroids to that patient? Raise your hand.
- They're on the floor.
- Okay? If I tell you they're covid positive you give steroids?
- Yes, a hundred percent. What if I tell you they have flu?
- No one is overwhelmed. Yet your your instinct is good because the psi, for that patient is 83.
- So I do think we can use some objective measures. I think that Crp is probably the best we got right now in terms of bio marker clinically available because we have to make the decision quickly. This is part of the problem, and so on a practical level. The quad screen is incredibly helpful, right? Because we can make decisions really quickly.
- And we need, I think in this case timing is critical and getting it in early. That's probably other. Take home from Cape Cod versus the other. Right? So it still has to be the right patient, and we have to be judicious, you know. Maybe what we need is a glucocorticoid stewardship team which is headed by Id, and so, instead of you know, they can call you from Po Bank and Dexametha Zone.
- Would you do that, Patrick? Are you really would love to? Okay not cool. So thank you so much. Thank you. Yes thanks for coming here. Good to see you.