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TRANSCRIPT - GR 01 24 25 *"**Updates on Lupus**"* guest speaker Michelle Petri MD, Johns Hopkins

Internal Medicine Grand Rounds

- All right. Welcome to medical grand rounds, Brian Newtlaud. We're delighted to have Dr. Michelle Petrie with us here from Johns Hopkins to speak on. Update on lupus.
- Excuse me.
- Okay. I'll just roll through our Cme disclosures Dr. Petrie's presentation objectives here, and I think we'll you'll see those again in a moment.
- Disclosures as well.
- and then cme credit code for faculty as well as ways to claim credit. I'll turn it over to Dr. Shaina Hassan, who will introduce Dr. Petrie.
- Well, good afternoon, everyone. It's my pleasure to introduce our grand round speakers for today, Dr. Michelle Petrie. So related to Dr. Bill Petrie. We're very excited to have her here, so she received her medical training from Harvard Medical School, and then completed her Internal Medicine Residency at Massachusetts General Hospital. She then went on to complete fellowships in allergy and immunology, as well as rheumatology at Ucsf. Before joining Johns Hopkins in 1986, where she then obtained her master's in public health, and has been there ever since.
- Her major role in nearly the last 4 decades at Johns Hopkins has been the principal investigator of the Hopkins Lupus Cohort, which currently consists of over 2,700 patients, and this is a longitudinal study of morbidity and mortality in patients with Sle. In addition to the current co-director of the Hopkins lupus pregnancy center the cohort has made significant contributions to the understanding of corticosteroid toxicity and sle the preventative role of hydroxychloroquine and the pathogenesis of accelerated atherosclerosis in this population and additionally, she served as a mentor for hundreds of students, residents, fellows, and faculty, over the last 30 years, providing her expertise in both clinical and translational research in Lupus, so we're very pleased to have her join us for grand rounds today so please join me in welcoming Dr. Petrie.
- Thank you.
- So Bill Petrie is my little brother.
- Now, here are the disclosures and the objectives that you already saw. So I want to start with thinking about Lupus as the tip of the autoimmune pyramid.
- Now, down at the bottom are autoimmune serologies.
- Do you know how many normal young women have a positive ana guesses?
- It's 20%.
- So please don't ever consult rheumatology for a positive Ana.
- Now, just above that level are the localized autoimmune disorders, and every specialty has a handle on those right. So in gi, it's primary biliary cirrhosis or inflammatory bowel disease in endocrine. It's autoimmune thyroid disease. What's really fascinating is why don't the localized autoimmune disorders always evolve into a systemic disease. It's probably a different Hla disease.

- Now, rheumatologists don't get involved until we get to the systemic disorders. So you see, at the next level, undifferentiated, connective tissue disease. What is that when I tell patients they have it, they say to me, oh, another doctor told me that was a garbage diagnosis. But it's not a garbage diagnosis, it's defined. It's people who have evidence of systemic autoimmunity. But don't meet the criteria for one of our named diseases like rheumatoid arthritis or sjogren's, and it might be, for example, Young who has an Ana and Raynaud's or Ana and Arthralgis, but never gets worse. And in fact, this has been studied over time. Only 10% of people with Uctd will evolve into a more serious named illness. Now, next question for you how many women in the United States have? Uctd.
- What if I tell you? The question was answered by lawyers? Now you're getting worried. But it was actually the lawyers who were in charge of the silicone breast implant lawsuits. They finally did a case control study that actually made it into the New England journal of Medicine. So about 5% of the general female population without a breast implant has a Uctd, so that's not rare, either. That means you have these patients in your clinics but once someone has a named illness, then they usually get to rheumatology. I put Lupus at the top of this pyramid. But what are some of the systemic autoimmune diseases that are more frequent than lupus?
- Sjogren's is probably the most frequent rheumatoid arthritis is certainly more frequent than lupus.
- Now, how many people do have lupus?
- Well, this was work done by the centers for Disease control, and they found that 200,000 people have lupus. So it's still quite a rare disease, isn't it?
- But, boy, does it have an impact?
- So in this study, Lupus was the 5th or 6th leading cause of death in young women of color.
- Now, once you know that now you're going to be very worried about a newly diagnosed patient with lupus.
- But I want you to forget those patients that have a positive ana and fatigue or chronic pain. I'm going to promise you they don't have lupus. What do they have.
- They have fibromyalgia. Remember, fibromyalgia is not autoimmune. About 3 to 4% of American women have it
- Ana and pain fatigue.
- You should handle rheumatologists. Our clinics are booked up, we do not have time for fibromyalgia.
- So here's my rule. The patient must earn the diagnosis of lupus with objective findings due to lupus inflammation.
- Lupus is not a gift diagnosis. You know. The person is feeling bad. I don't gift them with a diagnosis of lupus. It's such a serious diagnosis. Do you know, if the word lupus is in the patient's medical record, they can't get life insurance.
- So there are big impacts.
- But now I have to come full circle. So people who have lupus can have chronic pain and fatigue.
- This has been such an issue that we now have to separate the symptoms that a person with lupus has into 2 groups. So the type, one symptoms are those that are due to inflammation, like rash or synovitis or nephritis, and the type. 2 symptoms are from central pain, sensation so nerve to brain pathways, and those are the chronic pain, fatigue, brain, fog, insomnia, anxiety, depression, symptoms, a whopping. 1 3rd of people with true sle also have fibromyalgia and you can imagine

how disappointed a patient is if I tell them their lupus is under good control, and they still feel awful from their fibromyalgia. So not only must we understand this, we have to explain this to our patients as well.

- So what are the objective manifestations of lupus? These are the slick criteria to classify lupus. And what's different about these criteria is they are computer generated.
- This is not a group of gray-haired physicians getting together in a room and coming up with criteria. The computer decided this, and you'll see that the 1st 4 are cutaneous manifestations, and I'll later show you those in photographs.
- But one is acute, cutaneous lupus, sometimes called the malar rash or subacute cutaneous lupus, now subacute cutaneous lupus is not limited to lupus. A whopping. 50% of patients with this rash have it due to drugs.
- What is the drug that is mostly responsible for this in the United States.
- Come on, somebody must know it's proton pump inhibitors. So proton pump inhibitors are not benign, you know. They also contribute to chronic kidney disease and osteoporotic fractures. We spend a lot of time in our lupus clinic transitioning people from Ppis back to h 2 blockers. Now the next 4 criteria are different organ systems. So synovitis serositis, renal and neurologic and the last 3 are the 3 different hematologic cell lines. So hemolytic Anemia, Leukopenia and Thrombocytopenia. This is the clinical manifestation list. The person must have at least one of these and then they have at least one of the autoantibody list, but they have to total 4 things before we classify them as having lupus. Now Ana is here. We can't get rid of the Ana but it is true that 5 to 6% of people with real lupus are negative for Ana, but usually they have other autoantibodies.
- Now the next one is anti-double stranded DNA. And you know that's specific for lupus. The next one Sm does not stand for smooth muscle.
- What autoimmune disease is associated with anti-smooth muscle?
- It's liver.
- It's autoimmune liver disease. Isn't that weird? Why is it called smooth muscle when it's a liver autoantibody? But the anti-sm here stands for Smith and this is a wonderful history of lupus story. This goes back to Mo Reichland, who was a professor in Oklahoma and when he discovered autoantibodies he named them for the patient in whose serum he found them. So this is actually a Mrs. Smith, and Roe is named after a patient whose name was Rose, etc, etc. I think this is a wonderful story when our patients volunteer for research. Isn't it nice to memorialize their contribution? But you realize it's not hipaa compliant. We can't do this anymore.
- Now, the next set are very practical. They're anti false, lipid antibodies.
- Now, yes, 50% of people with lupus will have one of these antibodies. But if you think about antiphospholipid syndrome, half of those patients do not have lupus, and you're going to meet them in the emergency room, so if a young person comes into your er with a 1st dvt or a 1st stroke, do you know that about 25% of those patients have antiphospholipid syndrome, and if you don't send off that lupus anticoagulant assay, you're going to miss them.
- And for that patient with a Dvt you're going to mistreat them. Because what are you going to start a doac? Right? Well, please never use a doac in Aps. There's actually an FDA warning now that Doacs are insufficient because they don't protect Aps patients from arterial events. So it's still old fashioned warfarin the rule for Aps.

- Now, the next one is low complement, and you know that's not specific for lupus, but it's a big clue when it does occur, and then the final one is an antibody against red cells called the direct Coombs test. It's not apostrophe. S. It's actually Bs. It is named for the doctor who discovered the antibody.
- Now for some show, and tell. Recognize it when you see it.
- So what is this?
- Right? It's the malar rash. Now, it's obvious here, isn't it? Because you can see that it spares the nasolabial folds and below the nares.
- But are you a little worried because doesn't it look awfully pustular?
- Did anybody think, oh, could this maybe be acne, Rosacea. So you still have to be careful. But it's the sparing of the nasolabial folds and below the Nares that makes it clear that this is acute, cutaneous lupus.
- This only occurs in Sle.
- You cannot treat this by slapping on a lot of topical corticosteroids. You have to treat this with systemic therapy. What is the drug that we're going to use.
- We all learned how to pronounce it right at the beginning of the pandemic hydroxychloroquine right? All those syllables, but probably everybody in our country knows how to pronounce it. So this person needs hydroxychloroquine.
- But what if it's not happening right in front of you, or the person hasn't taken a perfect photograph then you have to know some questions. So your 1st question is, when does this rash occur in terms of sun exposure?
- If the person answers the same day, it's not lupus requires activation of the inflammatory cascade. The autoantibody has to bind to the autoantigen. You have to start inflammation. That doesn't happen on the 1st day. So 1st day rashes are usually solar urticaria. If it's small itchy bumps or a polymorphous light eruption or a blush flush those kinds of things. Your second question is, how long does it last?
- Lupus rashes because they're from inflammation will last for days to weeks. A transient rash can't be lupus.
- And your 3rd question is, is it raised? Obviously the lupus rash is raised, it has texture to it.
- Things like flushes and blushes are not raised, but other inflammatory rashes are so Rosacea is raised, seborrheic dermatitis is raised. Sometimes I, as a rheumatologist, will be stumped. I won't know, and either the patient's rash will need to be biopsied right then and there, or I will say to the patient, the next time you have the rash message me. So I get you in quickly for a biopsy.
- Now, what is this rash discoid right now? This is a worse rash because the inflammation is in the deeper layers of the dermiss so when it heals it heals the same way. A 3rd degree burn would heal with this kind of hypo and hyperpigmentation, and the hair follicles are permanently gone, and you get an idea how exquisitely photosensitive this rash is because it involves the inside of her ear.
- You know. How do you get enough sun in there?
- So this is very characteristic.
- But sometimes it's initially misdiagnosed as a fungal infection or something else? And can you imagine how devastating it is? I will tell you what happened when our outpatient center opened at Hopkins over 35 years ago, I said to the administrator that I needed mirrors in my exam rooms and his initial answer was, Oh, no, we're not going to pay for that. And I said to him. You have to. My ladies need to have a mirror because they have to put their wigs back on after I've examined them.

- And when he heard that, he agreed. And there have been mirrors in all the rheumatology exam rooms ever since. But can you imagine you're 20 years old and you're going to wear a wig the rest of your life, and the scars on the face, hands, and forearms. You have to hide those with cover up makeup. So this is devastating.
- Now, 80% of our lupus patients will have some sort of cutaneous involvement. A whopping 90% have joint involvement. When you look at this photograph. You're going to think this is rheumatoid arthritis, because you can see the deformities, can't you? The ulnar deviation, the z deformity of the thumb?
- But what's different about lupus arthritis is. If you and I could reach into this slide we could straighten the fingers. The deformities in lupus arthritis are reducible. It has a nickname. We call it Jacouds. But ultrasound studies have shown us that lupus synovitis mostly affects the second and 3rd Mcps. So I want to show you one of the Hopkins tricks. Look for the valley there.
- If the valley is missing, you're probably finding a patient with synovitis in lupus. It's not as exuberant as rheumatoid arthritis. It may not look like a big mountain. You're just going to find loss of the valleys.
- So let's go back to some basics. What causes lupus.
- So this cartoon says, figuring out the human genome map was easy, the hard part was refolding it.
- We, as taxpayers all paid for the human Genome Project, which, by the way, came in before the due date, how often does that happen? But we learned a lot now the big peak there in this Manhattan plot is the Hla system, but we learned from some of the other peaks some of the other things that were very important, including the interferon pathway. B cells. Immune complex processing bottom line is lupus is half genetics, but it's not a mutated gene.
- These are alleles that all of us may have and the more of them someone has, the greater the genetic predisposition to lupus. And, in fact, we think in pediatric lupus. Those are the people who have the greatest genetic predisposition.
- So if lupus is half genetics, it follows it must be half environmental. And of course sun is one of the big environmental precipitants. But, in fact, early childhood infections play a big role as well, and the early childhood infection that's been incriminated is Ebv.
- Now you probably memorized a list of drugs that cause drug-induced lupus. And by the way, they're drugs, we hardly ever use anymore. Right? Hydralazine, procanamide, isoniazide is still around. But it turns out that there are drugs. We currently use that cause drug-induced lupus. And those are things like minocycline anti-tnfs. And I've just told you about proton pump inhibitors.
- But interestingly, the drugs that cause drug-induced lupus do not cause sle but immune activators can cause sla, and that includes the antibiotic the Sulfa antibiotic that we call Bactrim or Septra, but in addition, Echinacea.
- Now I had to find out about echinacea from my patients. I was hospitalizing people with lupus flares, and after the 3rd patient told me that they had started to take Echinacea just before the flare. I thought I better look into it, and a good place to look into side effects of supplements is the German website because they don't allow supplements over the counter. All supplements are prescribed by physicians, and so the side effects are there, and Echinacea has been known for a long time to be an immune activator. It's why it was studied for the common cold. For example.

- Now, at the bottom you see the effects of environmental pollution which do play a role in lupus and the incidence of lupus has doubled in the last 20 years, you know, a lot of autoimmune disease are are on the increase. Did you know that Ibd is?
- But we think that that must be probably from environmental pollution.
- Now, why is lupus more common in women?
- Does anybody want to answer? Estrogen turns out it's not estrogen, you know. Sometimes we preach things for decades, and it turns out we're wrong.
- But my colleagues in the basic science part of Hopkins were part of this discovery. It's not estrogen. The reason that women are more subject to lupus turns out to be due to incomplete X inactivation and that can lead to an increase in a long non-coding Rna that's called X ist and Xist is a Tlr. 7 ligand. What that means is, it can bind to plasma cytoid dendritic cells and start the interferon cascade that can lead to Lupus. So isn't it fascinating that we finally have figured something out? After what is it? You know? 120 years of saying it was estrogen.
- So how does Lupus start?
- This was discovered by the former chief of rheumatology at Hopkins and his wife. So this is Anthony and Livia Rosen, and what they found was the 1st break in tolerance happens at the level of programmed cell death.
- So what you see in this photograph is a cell undergoing apoptosis, and those little bodies around the cell contain the proteins that people with lupus recognize as foreign. So that's where the phospholipid proteins rola rnpsm are now in you or in me. We have millions or billions of cells undergoing apoptosis every single day and our macrophages know how to gobble them up in a non-inflammatory way.
- So we don't break tolerance, but someone who's genetically predisposed to lupus.
- We'll gobble them up in a pro-inflammatory way releasing pro-inflammatory cytokines like Tnf, that then lead to further autoimmune consequences.
- And then there's a feed forward loop. Now, what I'm showing you here is actually the normal immune system. So this has to work in you or in me.
- But what happens in lupus patients is that it's activated all the time. If we start at the very top our plasma, cytoid dendritic cells are essential. Without them we would not survive the common cold and the reason is they make interferon but a whopping. 50% of people with lupus have the interferon gene signature, which means their interferon is on all the time.
- It's nothing to do with an infection. It's always on red, alert and then that can activate the myeloid dendritic cells that present antigen to our T cells.
- Well, if you're presenting self antigen, of course you're going to be in trouble.
- But in addition, the myeloid dendritic cells make a protein called baf.
- which is a survival factor for all B cells. But in particular for autoimmune B cells.
- And of course, everybody here knows that B cells are a problem in autoimmune disease. They're making, not just autoantibodies, but cytokines. And then these complex to the self antigen, those immune complexes can then activate plasma, cytoid dendritic cells through those Tlr receptors. Remember, that's where exces plays its role.
- Now, probably people with lupus enter this feedforward loop at different places. Some people probably have b cell lupus. Some people have t cell lupus or plasmacytoid dendritic cell. Lupus. We don't know.
- We don't have a biomarker to tell us how they get into this, but once they're in, can you think of this as an equal opportunity loop. There are many different places. We can interrupt this loop to try to slow down their autoimmune process, but the minute

we do that, of course, we're taking away from the normal functions of our immune system, fighting infection and early detection of malignancy. So there's always a price to pay.

- Now, here's 1 of the prices I run into trouble sometimes when my talks get Cme reviews.
- Yeah, I had one company say to me, I couldn't say this.
- By the way, what is the definition of a poison?
- It's something you give that can kill the person.
- I think I'm completely accurate here. But for that particular Cme. Review I had to put down. Prednisone is a problem. Now, many people think that a person with Lupus gets a free pass to prednisone because lupus is such a bad disease. But in fact, I'm here to tell you that 80% of the permanent organ damage that happens to someone with Lupus happens because of their prednisone.
- You think that's fair.
- I want you to feel really guilty if you ever write a prednisone prescription.
- So how bad is it? Well, this is one of the 1st studies that I did. It's longitudinal regression. And for those of you who are interested in biostatistics, what's really important is when you're giving something for a reason. So I'm not giving prednisone for the fun of it. I'm giving it to treat active lupus you have to find out. Is it the active lupus that's responsible for the bad outcome? Or is it the prednisone? And so that's called adjusting for confounding by indication?
- So this was one of the very 1st analyses that could do that. And it was because Hopkins has a wonderful school of public health and this technique was invented not to study lupus, but to study HIV infection, so we just immediately borrowed it. And what we discovered is, if the maintenance prednisone dose is above 6 milligrams. There's going to be a 50% increase in permanent organ damage right there.
- And that's why we circled in red that we thought that we had to keep everybody's prednisone below 6 milligrams. Even when we do that, there's going to be a 16% increase in permanent organ damage, particularly osteoporotic fractures.
- Do you know what is the most common site for osteoporotic fractures from Prednisone?
- It's going to turn out to be the back.
- Can you imagine how painful that is because most patients will have multiple vertebral fractures.
- But prednisone also increases the risk of cardiovascular events. So these models had to include all the cardiovascular risk factors and you can see if the prednisone dose is 10 milligrams, there's a fourfold increase, and if it's 20 milligrams, I'm sorry. 2.4 fold increase. If it's 20 milligrams, there's a 5 fold increase in cardiovascular events.
- Cardiovascular events are the second most common cause of death in people with lupus.
- So, of course we need to avoid prednisone for all these reasons. But now I want to bring it home to you because you said, I don't have lupus. This is a slide for you. This is based on the Swedish general population registry.
- Glucocorticoids kill normal people in Sweden.
- And look at that dose response. So this is just being above 5 milligrams for more than 21 days there's a twofold increase in the hazard ratio. You can see that there's

a clear dose response, and at the highest dose. 2 reasons stood out, of course, sepsis but also pulmonary. Emboli.

- Why did you know that steroids are prothrombotic?
- Now you're worried right. You're not going to let anybody prescribe prednisone for you.
- So what do we do? Our goal in treating people with lupus is to get the disease under reasonable control mild activity, and not to let the prednisone dose get above 7.5.
- Now this has now been amended. So last year the European rheumatologists published their lupus guidelines. And now they've said that the limit on prednisone has to be 5 milligrams. So they've come around to my study that you saw was published decades ago. So you see, I never give up. I keep saying and saying, and then I'm very happy when people listen now, if we could keep people with mild activity and low dose prednisone.
- How much damage could we prevent? Well, we could prevent 50% of later organ damage. So if we're going to be perfect.
- There has to be no lupus activity and no prednisone. We're not perfect.
- So what are our current treatment approaches?
- Well, the 1st is hydroxychloroquine. Now hydroxychloroquine is an example of listening to patients. Hydroxychloroquine was invented back in World War 2 and was widely used in the South pacific as an anti-malarial and the soldiers and sailors came home, and those who had lupus and rheumatoid arthritis didn't want to stop it. They're going to say lupus and rheumatoid arthritis, soldiers and sailors. Yes, back in World War 2. There were very few departments for medical conditions so they came back, and they said to their doctors at home. I need to stay on this medicine.
- That's how it was originally learned that hydroxychloroquine helps both lupus and rheumatoid arthritis. So please listen to your patients. Sometimes they're going to not come up with some junk from the Internet. They may actually have something important to teach us. So why is hydroxychloroquine so important. It helps skin and joints. It prevents 50% of flares. But I want you to think of it as a preventive medicine.
- It prevents Lupus from spreading into the kidneys or the brain.
- And in particular, it's the only medicine we have that improves the survival of people with lupus, probably because it lowers the risk of cardiovascular events and diabetes.
- and if someone has to stop their hydroxychloroquine, their risk of dying goes up 4 fold.
- So I want people on this medicine forever.
- But every medicine comes with some baggage, right? So what problems can hydroxychloroquine bring? There is a risk of retinopathy the risk after being on it for 16 years is 10%.
- Now, if your eye doctor said to you, this medicine can make you go blind. Are you going to want to take it.
- No, so I get very upset with ophthalmologists that say that to a patient I've never had a blind patient from hydroxychloroquine, and I've been using it for over 40 years.
- But I do have blind patients with lupus.
- They're blind from lupus retinitis or lupus scleritis or hypertensive retinopathy or stroke or diabetes.

- All those things I just listed are helped by hydroxychloroquine.
- Now, why do we have no blind patients from hydroxychloroquine? Because we know how to monitor the retina. Does anybody know what test I'm showing on this slide?
- Anybody here interested in diabetes? Now, this is the Oct. This is like taking a snapshot of the retina and you and I can interpret it. This is important, because back in the old days, before electronic patient records, nobody could read ophthalmology notes, I'm serious. We couldn't read them. But this we can read ourselves. So what is it showing? Here is the normal retina. And you see that nice dip?
- That's a normal retina.
- The photo at the bottom is a retina with hydroxychloroquine retinopathy. The dip is gone.
- And what do you see instead, what does that look like flying saucer, and, in fact, that's the name of it. The ophthalmologists have named it the Flying Saucer Sign. So if you see the Flying Saucer sign that patient has deposition in the retina, and they have to stop their hydroxychloroquine.
- This is reversible at this stage. It's 1 of these, no harm, no foul issues. But we have to do a lot of reassuring to the patient, because adherence is everything. The patient's scared of a medication. They decide not to take it. They can't benefit from it now. Only about 30% of people with lupus are going to be able to manage on just hydroxychloroquine. The others have to have things added. So we add a lot of oral immunosuppression, and the only things that are FDA approved on this slide are circled in red. So we depend on the organ system to tell us what to add.
- So if someone has skin or joints, we often add Methotrexate. If it's kidneys, we add mycophenolate. If there's a pregnancy plan, we have to use azathioprine because it's the only one allowed in pregnancy.
- But about 25% of patients will need biologics and the biologics actually attack different mechanisms of action. So Rituximab, of course, is a B cell depleter.
- But it turns out in 2 clinical trials in lupus. It didn't help renal or non-renal lupus. The only reason it's still on this slide is, it has a niche. It helps hemolytic anemia. It helps thrombocytopenia. It helps lupus pneumonitis, and it helps a terrible complication of antiphospholipid syndrome, the catastrophic form of aps. So I'm going to tell you about 2 other biologics. Bulimumab attacks. Baf. Do you remember Baf was like that factor that kept B cells alive.
- And Anifrolimab attacks the interferon system.
- So let's go into why, we're using these. So here is the benefit of belimumab for non-renal lupus, but only in the subset that have anti-DNA or low complement. Why does this matter? If the person has low complement or anti-DNA. It tells me B cells are driving their disease. And you can see there's about a 20% delta that doesn't seem like a lot, does it?
- But this one is very safe, does not increase malignancy, and does not increase serious infections, and does help of skin and joints.
- Here is Anifrolimab. This is the one that attacks the interferon system.
- And here what you see are the results for skin.
- So it does work very well for skin lupus, and it works within a month. So if you were that person with Discoid Lupus would you want it?
- Of course, but you know we have to fight for these very expensive biologics.
- But I'm going to challenge you today that, in fact.

- our greatest unmet need in lupus is renal lupus.
- Now, why do I say this?
- I want to show you the data. These are deaths from lupus nephritis, not just going on dialysis deaths. And I want you to see that it looked like we were doing okay until 2015. And suddenly the deaths are going back up. Now this is pre-pandemic. No one has a good explanation for this. But, boy, it sure tells rheumatologists and nephrologists because we share care of lupus nephritis patients that we're not doing enough if more people are dying from lupus nephritis and a lot has been learned from past clinical trials. Right now, at the end of a 1 year, Lupus nephritis, clinical trial. The goal is what's called a complete renal response.
- It's defined as achieving 500 milligrams or less urine protein.
- Is that normal?
- No. What's normal in your lab.
- probably less than 200. Right?
- I give the analogy of what if you had cancer and you go to visit your oncologist for the 1st visit, and the oncologist says, my goal at one year is to leave you with cancer.
- Would you get up and walk out and find another specialist? Yes. Why does anybody want to be left with lupus nephritis at one year? So here's the proof from a clinical trial, if someone has no response at all, and really everybody's on dialysis. 10 years later, if you have one of those partial responses like you get to 500 milligrams, over half of people are on dialysis. The people who really escape dialysis are those people who go back to being normal.
- And so I would posit that part of our problem is, our clinical trials have a wimpy outcome, and we need to do better.
- So how are we doing better? This is the study of Belimumab for lupus, kidney disease. Remember, it's going to block back the B cell survival factor. At the end of 2 years, people who were on it were about 11% more likely to have achieved a complete renal response.
- And here's our other FDA approach. This is calcineurin inhibitor but it's easier to use than tacrolimus, because it has better pharmacokinetics. So it's a fixed dose. You don't have to measure both the trough and peak levels. And at one year there was an 18% Delta. This one works fast. It works within one month, and it works on podocytes. And for the nephrologists here, you know this, but for the rest of us. Podocytes are very leaky when people have inflammatory renal disease, and they're one of the reasons that there's so much proteinuria.
- So this one is FDA approved and particularly beneficial for people with high levels of urine protein.
- But now we have to redefine lupus nephritis because lupus nephritis is really an example of chronic kidney disease.
- And it's this nephrologist, Professor Anders, who brought this to my attention, because what he teaches is by the time I identify the person who has lupus nephritis. She has already lost 1 3rd of her nephrons and she's never getting them back.
- Nephrons do not know how to reproduce now initially her remaining nephrons, hypertrophy, and kind of carry the load, but then they start to wear out. Now in you and in me we're going to lose nephrons and podocytes as we get older, but we have enough in reserve that we can get to 100, and I hope we all get there and not be on dialysis.

- Now, if there was a perfect world, and that woman with lupus kidney disease goes into remission quickly. Remember, she took that 1st hit. She lost a 3.rd But then, you know, she'll not be on dialysis until she's 100.
- But that isn't how it happens. It takes forever to get a renal response. That's why our outcome at one year is so wimpy, and the average lupus patient has flares, and every time they have a flare they're going to lose more nephrons. So they take that initial hit.
- They're going slowly in the right direction, and they have another flare and oops.
- They're on dialysis. So Professor Anders is in Germany, and he teaches that all of his patients are going to be on dialysis by age 70. In the United States our lupus nephritis is much worse than European nephritis. And so our patients are going to be on dialysis sooner.
- So we have to think about lupus nephritis, not just in terms of how to treat the inflammation, but how to prevent worsening of chronic kidney disease. And it turns out there was a big surprise with Belimumab. Remember, it's just blocking bath but it turns out it protected the Gfr.
- And, by the way, this graph was in the supplement.
- This was a New England journal of medicine paper, and the most important finding was in the supplement. Most of you don't even know how to get to the supplement of the New England Journal of medicine. Maybe you have to be a paid prescriber to get into it, but it's the most important finding what a surprise
- something that is affecting the B cell pathway can actually protect the Gfr.
- But everybody here knows another way to protect the Gfr. What's the other way?
- Sglt 2 inhibitors? So has anybody looked at those. Yes, in China. Now this is a very small study, right? 38 people but the one you know of as Farziga did seem to protect the Gfr. But it did not reduce the proteinuria in studies of Sglt. 2 inhibition in diabetes, for example, there's also a reduction in proteinuria. So we're going to have to learn more about sglt 2 inhibition in lupus. It's fascinating, though, in an animal model of lupus. Sglt 2 inhibitors reduce lupus autoantibodies isn't that weird because you don't think of them as anti-inflammatory.
- But we've had a revolution.
- And the Revolution again started with a paper in the New England Journal of medicine, but not a clinical trial. It's n of one.
- It's 1 patient being treated by Georg. Sched in Germany with cellular therapy.
- CD. 19 directed cellular therapy. So it's going to get a broad swath of the B Cell family.
- Now, you can see. She came into this study with multi-organ lupus activity and very quickly went into a remission.
- A miracle happened when her immune system came back. It had reset to a naive, immune system. It didn't come back as lupus.
- That is a miracle, because, believe me, it didn't happen with Rituximab.
- It happened with cellular therapy. Why, it's thought to be that with cellular therapy you achieve a much deeper B cell depletion.
- Now, I don't want you to think this is easy to do. This costs $500,000 per individual patient and Georg Shett has now treated 8 patients, and all 8 with lupus nephritis have gone into a remission. This particular lady has been in it the longest. She's over 4 years and the remissions are there, even though all the lupus antibodies are still present because many of the lupus antibodies are being made by plasma cells.

And this kind of therapy is just getting B cells that's really confusing for those of us who trained in immunology.

- How can you have a remission, and the auto antibodies are still there. It's some weird new part of tolerance that we have never understood.
- But it's not all good news. You know how initially everybody gets very excited, and then things have to settle down a little bit. So here's the part we have to settle down. So here on the left is the German experience, and I want you to look at. One patient did have their proteinuria come back.
- But on biopsy it was something called a lupus podocytopathy, a very rare kind of lupus kidney disease that quickly got back under control with some steroid.
- But here on the right is another company and they're also looking at CD 19, directed cellular therapy, and you can see very clearly visually, can't you? The protein is all over the map. This isn't a nice, simple picture like in Germany.
- And then in the middle is the approach that immunologists would have favored. It's called bispecific. Let's not just target B cells. Let's target plasma cells as well. Now, when you do this, they're not going to be any immunoglobulins left. You have to support the patient with intravenous immunoglobulin until the immune system resets.
- Does this look like a good result to you? Is that proteinuria all over the map?
- But can you see another problem? Now, the nephrologists here know this already, but Proteinuria isn't just from inflammation.
- It can also be from chronic damage.
- And unless a second biopsy is done, how do we know for sure?
- So this is a huge problem. Now in lupus nephritis studies trying to force into the study design a protocol kidney biopsy at one year, because we know if lupus kidney disease is in remission, the immunofluorescence will be gone and on electron microscopy there will be no immune complexes without that we don't know for sure if the patient is in a remission or not.
- So this is a wonderful opportunity, not just in lupus, but in other autoimmune diseases to see what the effects are of deeper B-cell depletion.
- But in reality we have to be able to scale this for those 200,000 patients. It can't be $500,000 a year. We may be able to achieve something similar with something that are called T cell engagers. The equivalent of a biologic attached to a T cell. So the T cell can drive the biologic deeper into the tissues. So more to come. But now you'll know why everybody got so excited about cellular therapy.
- Now I work with a wonderful faculty member named Andrea Favo, and we're trying to be able to follow lupus nephritis activity in real time without having to do a kidney biopsy all the time. So this is what we found in the urine proteome, and everything that is circled are urine proteins that are more predictive of one year outcome than the urine protein to creatinine ratio is. And these have identified pathways that we didn't know existed. So one of them is CD, 163. That's from macrophages. It tells us macrophages are involved. Another one is called interleukin, 16.
- An inflammatory Cytokine that no one even knew was in the lupus kidney until we did this work, and a 3rd are pr 3 proteins. Now the rheumatologists and nephrologists know all about that. Those are part of Anca Associated vasculitis.
- Nobody knew. They were part of lupus kidney disease.
- So now think of this. We've got 3 new targets that might be amenable to treatment, but in addition, now, every time we see the patient we might be able to adjust their therapy up or down depending on what this urine proteome dipstick told us. Now it's

going to take us 5 years to get this into the clinic. But can you imagine how exciting it would be to be able to change therapy rapidly over time to ensure that the patient's adequately treated, but equally important to make sure they're not being overly treated.

- Now, I always like to add with art because I come from a family where we all love art. This is a painting by El Greco of St. Sebastian, you know, dying from multiple arrows. But it reminds me how challenging Lupus is. So 1st you look at the suffering on the saint's face.
- That's the suffering from those type. 2 symptoms that people with Lupus have. But then think about all these arrows in the heart and here's an arrow in the kidney, and then the hypertension arrow.
- Oh, by the way, Arrow in the lungs, 10% of lupus patients have pulmonary fibrosis. I want to tell you about the hypertension. Arrow hypertension is, of course, amenable to treatment.
- It's an independent risk factor for cardiovascular events in people with lupus. Our goal needs to be 120. But, by the way, that's not just a lupus goal. That was the goal in the sprint study in the general population 120.
- Our problem is about half of our patients miss that goal, and you know why they missed the goal often it's forgetting to take their medications or dietary indiscretion. Can you imagine what it's like to be a rheumatologist? Our guidelines have taught us that we're supposed to be in charge of the cardiovascular risk factors. So we're trying to handle the lupus. We're trying to handle all these comorbid factors. We're trying to judge treatment. Response.
- This is a challenging field, but I have never, ever regretted becoming a rheumatologist. I am never bored. Every clinic I learned something new. So if any of you are interested in rheumatology. We'd like to see you come to Hopkins for an elective.
- Thank you very much for your attention.
- Okay thank you so much, Dr. Petrie, so I'll open up with the 1st question. So I was thinking about how you were talking about how Lupus is half environmental, half genetics. And then I was wondering if you could weigh in on any of the patients you've taken care of over the last several decades, and whenever you have patients who decide to do something more focused on diet and lifestyle changes specifically, dietary changes and how that may impact their disease activity. Or if there's been studies that have looked into that.
- You know the problem with counseling patients about dietary things is, there's very little known. Scientifically, however, it is definitely true that the fecal microbiome is different in people with active lupus.
- There's a particular streptococcus that's there but we don't know whether intervening would help. However, you could intervene in 2 ways, you might intervene with a probiotic to help other bacteria grow, or an antibiotic to target a putative subset of bad bacteria, so that has to be studied.
- But what patients? Google is the anti-inflammatory diet. It's a book written by a holistic physician. It's never been tested in lupus, but in general, because of the increase in cardiovascular events. In people with lupus we think a heart healthy diet is the 1st way to start but in terms of things that we know are bad in lupus. Did you know alfalfa sprouts are on the no-no list? Have you ever had a meal of just alfalfa sprouts? But it turns out there was a monkey experiment, and so they were fed. Just alfalfa sprouts and an amino acid in the alfalfa sprout called Carnavirine led to

Lupus, you know. So I tell patients if they go to the salad bar, you know, just don't have a whole plate full of alfalfa sprouts, so there's not a lot that I can teach a patient scientifically, but maintaining a normal weight is really important because it turns out adipose tissue is not benign. It makes pro-inflammatory adipokines.

- and so in mice with lupus, who are put on a starvation diet. Their lupus gets better. Now, of course, we're not going to put any human being on a starvation diet. But it's an example that maintaining ideal weight is a good idea. When people have lupus, and I cannot tell you what an exciting time it has been with the glp. One inhibitors, because my patients, many of them, have been unsuccessful with weight, loss for decades, and when patients make such rapid progress.
- They are happier.
- I wish that these things didn't have to be so expensive and to limit them
- so yes, people can say, doesn't a glp. Inhibitor cause gastroparesis.
- Yes, but that was from diabetes, studies. We haven't seen any problems like that in Lupus.
- Does my brother get to ask a question?
- I've never told you this, but when you went into internal medicine I thought everybody in internal medicine was as smart as you were. There wasn't any room for me, and so I'm glad there was a little bit of room. So.
- But you know the Tlr. 7 thing is so interesting. How much do you think, like collagen vascular diseases which are predominantly disease of women, are due to Tlr. 7. And is that leading to any new therapeutic approaches? So, by the way. This is also true in Kleinfelter's, for example, so that this is just true exist is important. I don't think it's been adequately studied.
- It explains the the estrogen hypothesis, and I don't know how important it's going to be in rheumatoid arthritis, sjogren scleroderma, for example, because so many autoimmune diseases are female predominant could we do something to downregulate excess? Well, of course we could. But estrogen isn't always bad, right? Maybe excess has some good functions, so I think more to come, but it's being very actively studied both at Hopkins and at Stanford.
- Thanks so much that was fascinating feature, primary care, doctor. Here I thought that mention of fibromyalgia and the increased frequency in the lupus population compared to the general population, was interesting. Is there anything specific about lupus that you think affects the development of fibromyalgia different than the Pathophys in the general population, and any different way we can target it.
- So it turns out that fibromyalgia shares some of the same genetic predisposition as lupus. So that may be the connection.
- But you're right. It could also be something that Lupus did to those nerve brain pathways that led to chronic pain, sensitization. And maybe it was something that happened very early in the course of their disease. It's not reversible by any lupus medication.
- And so I think that's what's frustrating to people who have lupus when they feel bad. They think it must be they're feeling bad from their lupus and I'm the one that has to tell them that it's not lupus, but a whole different pathway that's creating the fibromyalgia symptoms. Now, when there is a very effective treatment for fibromyalgia. Of course our lupus patients deserve it as well. But what's available now? All the medications that are used for neuropathy can have a role for fibromyalgia, and that includes, of course, things like Duloxetine, Pregabalin, Gabapentin.

- Amitriplin. So we use a lot of these. But movement also matters too. So I've been mentioning a lot of studies in the New England Journal of Medicine, but I'm going to mention the Tai Chi study because it was done by a Boston rheumatologist, and only had 40 patients in it. Nothing to do with lupus. General population study with only 40 patients with fibromyalgia, they were able to demonstrate a statistically significant benefit of doing Tai Chi every day. So it's very easy for patients, because there's a tape on Youtube called Tai Chi for arthritis.
- They can start very slowly, but they need to continue it. People tend to lose motivation. You do. One week of Tai Chi. You don't feel any better. You're going to stop. No, this study went on for 6 months. So it's very important to encourage patients to move.
- Please also recognize that 50% of people with fibromyalgia also have clinical depression.
- So, although antidepressants don't help fibromyalgia antidepressants, meaning Ssris could certainly help underlying depression sometimes I get a lot of pushback. You probably do, too. You tell a patient they're depressed, and they tell you they have a very happy life while the tears are rolling down their face.
- I have this happen very frequently. Depression still has a stigma. People think that we're saying to them that they're a weak person. and, in fact, what we're saying to them is, the brain can get sick just like any other organ.
- Why would we want to ignore the fact that that person's brain is sick, so please, primary care. Don't be afraid to tell a patient that they have clinical signs of depression and don't be surprised when you get the pushback. Be ready for that.
- No other questions.
- So I'll stay afterwards in case people want to ask me private questions. But thank you very much for the invitation.
- Okay.
- please let me ask that question at the institution.
- Yeah, yeah.