JEN-JAR LIN: Thanks. I really appreciate this opportunity to be here to discuss with you about the childhood nephrotic syndrome from a kind of more practical point. Is my voice loud enough, or too loud? OK. Let me see.

So, as you all know, nephrotic syndrome requires four elements. The first thing you start with is the heavy proteinuria. Now if it's correct, 24 urine, is more than 40 milligrams per meter squared per hour, or on a spot urine protein/creatinine ratio. That's two. Now these are 10 times more than normal.

Because there is a heavy loss of protein from the kidneys, that results in the loss and the reduced serum protein. Usually it's the low molecule weight. Now this is very important. It's low molecular weight protein got lost first. And for this reason, we use albumin as a marker for the degree of the reduced serum protein level. And usually when the serum albumin is 2.5 or less, then we say, wow. This is becoming a problem.

The third criteria is edema. And this is because when you have to reduced serum protein level, which will reduce the oncotic pressure, which I'll discuss with you later, that's causing the fluid shift from intravascular space to interstitial.

The fourth element, the criteria, is the elevated serum lipids. Usually it's the cholesterol. And this is because of the loss of the low molecular weight lipoprotein A, which is a protein you need to carry the cholesterol to the peripheral to be metabolized. So because of the loss of the lipoprotein A, you have accumulation of cholesterol and other lipids.

These are the classical four definitions for you to call a child has nephrotic syndrome. I want to warn you that edema is not necessarily present when a child has the nephrotic syndrome. Because if the child is dehydrated, you don't have the fluid shift to interstitial. You might not see edema.

So, what's wrong with the kidney that's causing the loss of the protein? Now, this is the picture of glomerulus. And that's a cartoon with a cross-section of the glomerulus. And it looks complicated.

But the glomerulus actually is the cell folding of a segment of capillary by a cell, like a neat ball. And you cut across in the middle. And that's what you see. And it still kind of looks complicated.

And the capillary group is held together by mesangium. So I try to explain to a student all these 25 years I've been in this field, and everyone looks at me, and say, what are you talking about?

Then one day, one of the students said, Dr. Lin, that looks like a small intestine held by the omentum. And I said, oh yeah. And then imagine the space around the capillary is a peritoneal cavity. That's it.

And then when I use that, everyone says, oh yeah, that's what it is. It's kind of sad I had to use the GI anatomy, to explain it. But that's exactly what it is.

And then you see that afferent arteriole that controls it by controlling its caliber, and also the efferent arteriole, which is shown on the other side that controls the blood flow through the capillary, and that determines the pressure across their capillary wall. That determines how the filtration process occurs.

Now if you look more closely about the capillary wall, you see that the square box on the left, closer up it looks like teeth. But from inside out, it's, an endothelium is there, basement membrane is there, and there is epithelial cell, which is just like an octopus with the feet landing on basement membrane.

Now all together, creating the filtration barrier, this is important because the integrity of this filtration channel, which we call the slit diaphragm, is controlled by all three elements there. I show you the cytoskeleton of the foot process and the basement membranes. Anything wrong with any part of this is going to cause protein loss. Again, start with a low molecular weight first. Then as the process is ongoing, your loss of protein happen.

So just by-- imagine this, well, what can go wrong with these proteins? The first come out, OK, so I'll say medications. The second one is was something wrong with the gene? Like the proteins just don't develop well. The third is the most common one, is somehow the immune system does not like any of these proteins, and produces immunoproteins and attacking them.

And these are the categories of nephrotic syndrome that form the base for the immunotherapy for patients with nephrotic syndrome. Now how are we going to classify these?

It's a syndrome. So it can be called for a meta-disease process, of course, just like any other organ. The first thing you see is the pathology which is shown on the left lower area. Minimal change disease, we call MCD, means that that microscopy was you don't see anything wrong with it. Only you see those teeth, I mean the foot process, it's effaced.

And then of course, you have the focal segmental glumerulosclerosis. Focal means that on the biopsy sample, you only see part of the involvement. Segmental means that's a part of the glomeruli, any scarring. And they are the membranes. And then nephropathy means that the membrane, the basement membrane, somehow is thicker than usual, is made of a lot of proteins.

So this will tell you the morphological changes. And in the past 30-40 years a lot of study is geared into this. They say, what can we do? What's causing it. Again that by itself is another list of etiology. That is a pathological classification.

And then there's a different type of classification. Of course, the easiest thing is well, is this a primary or secondary. And I'll show you the list of secondary nephrotic syndrome later. But you can see what's the timing of presentation, congenital means that it occurred before 3 months, and the infantile between 3 to 12 months, and childhood is anything other than.

Or it's more practically relevant is the clinical response to steroids. And this is actually the main approach of how we take care of the patient. Look at well, are they steroid-sensitive or steroid-resistant?

It's well known that a child sensitive to prednisone has a better outlook. Regarding what is underlying pathology, that's primary or secondary.

And among the sensitive nephrotic syndrome, you also can be steroid-dependent or frequently relapsing. And those are the definitions over there.

Another classification is pathology, just like I told you earlier. Another one is familial. So again, these can be confusing actually, because it doesn't really tell anything. Because it's one of these constellation etiologies. So you say, well, what am I going to do?

Now, these are the list of secondary. And as you can see, either it's from systemic infection, immune mediated, or tumor, which can secrete certain proteins that can change the glomerular permeability of medications. And obesity is was one of them, and it's a long list. So these are the things you have to think when a patient presents with nephrotic syndrome.

So let's go back to the idiopathy. Because idiopathy there for us, means that when you tell the parents, you say, well I don't really know what causes it. And they're going to look at you, and say, well, how come you don't know. And indeed, we don't know. Because we know that so many studies have been done which have shown that either it's a T-cell problem, or the B-cell problem, or this is the immune-mediated injury to the podocyte, which is the foot process of the parietal cell.

And not only this, we know that a lot of these problems, injury, is related to genes. So there's a gene mutation, in addition to many that gene modifier, microRNA, and environmental factors. Such as a lot of people are talking about gluten-free diet. And this is actually ongoing. And there's sponsored trials ongoing on that.

So all these things interact with each other, and cause nephrotic syndrome. Now, the reason we still don't know what's causing it for any specific patient, and we call then idiopathy, is that in the past 30-40 years we started the problem on the protein levels. And then we kind of called in a way the pathology, and try to make sense out of it. And say, what is the problem.

But because there's a lot of interaction among the proteins, it turns out that we don't know what that is. Still we call idiopathic.

So we try to find the cause of the idiopathic nephrotic syndrome from a different direction, from the gene level. Which is a lot easier. Once we know what is the gene responsible for the problem, then we can easily find out what the downstream protein problem is.

And that makes it very easy for us to design an intervention strategy. Because that's the main purpose. And I just tell you. These have just come out the past few years. And we are involved in a network that's involved with Duke. That's the first one that comes up. You can see that the second one is from Europe, the Italian group. And the third one is from Boston, Harvard. Just to give an example that's the directions we are going to.

So let's turn the gear to what happened, what's wrong when there is not enough serum protein. What kind of problem clinically will happen? Well, the fluid movement across the capillary is determined by something called Starling's Law. It is the balance between the oncotic pressure, which is holding the water within the vessel; and the hydrostatic pressure, which tries to push the water out of vessels. It's a balance between them.

So if you have a decrease in urine protein that would reduce oncotic pressure. That would make the hydrostatic pressure more dominant. And that's where the edema occurs. Also the sodium actually moves along the water. That's why we kept saying there was salt restriction on children with nephrotic syndrome is because we want to minimize edema.

Because it's the water movement. So it's gravity dependent. And it can happen or occur in any part of the body.

So what kind of problem can occur because of this shift of fluid? Of course, the first one is edema. Depending on where that is, it can cause if it happens in the lung or the pleural cavity, you can get pulmonary edema, pleural effusion. And cardiac would give you pericardial effusion. Ascites is something very bad, abdominal distention and pain. And bowel edema that can cause diarrhea, or even on genital area, and leg edema, and hypertension, of course.

So, the one common complication from nephrotic syndrome is swelling. And depending on where that happens, that can be significant or can be not.

The second one is the loss of many small molecular weight endocrine system binding proteins. For example, you know that in thyroid function, the thyroid binding globulin is very important to bind a hormone to carry them to the target organ for it to work.

Those are small molecular weight proteins. So we have a reduced the thyroid binding protein. Because of this, the total T3 or T4 will be falsely low. But you measure the free T4, it will be normal. But the TSH will be increased. And there has been a debate between nephrologists and endocrinologists well, are these patients really hyperthyroid or is euthyroid. It's a big debate there.

Another thing that we also got involved in [INAUDIBLE] status, it turned out that those patients with symptomatic nephrotic syndrome had a vitamin D deficiency. And then when they get into remission, some of them, vitamin D levels are normalized. Now it goes along with the loss of the binding protein, but some don't. So the question comes, why some do not recover their vitamin D level. And there are nutritional deficiencies, as you can see here.

So the third complication is the kidney, of course. You are losing water from the vessel. You've got hemoconcentration. The blood gets thicker, slower. And that reduces the renal perfusion.

In addition, the swelling can happen in renal parenchymal that press on the vessel. And also that you have the glomerular filtration that because of the reduced permeability, then you have a building of body waste. So this is actually the ATN is a very common finding. And of course you look at the BUN/creatinine. They will go up. And once in a while we see those very sick patients that we need to do dialysis.

The forth potential complication is infection. Again, there's a list there on the second wall, it will tell you what is the risk factor. These are all small molecular weight. In all, there is a decrease in the immune system to fight infections. And it literally can happen in any part of the organ.

I've seen patients with meningitis, a patient that has cellulitis, and let's say scrotal cellulitis because the swelling scrotum rubs against the thigh, to give you cellulitis. So anywhere it can happen.

The bacterial strains, most commonly it's a strep pneumo for some reason. I think that people feel this is the problem with the opsonization. But I'm no expert on that. So I just leave it there.

But gram-negative is possible. So if you suspect a patient, a child, with nephrotic syndrome has an infection, and you don't know what you're going to do. If it's not a UTI, you can [INAUDIBLE] a third-generation cephalosporin. That should be enough.

The thing that we don't like mostly with a high mortality is peritonitis. Because clinically it is very difficult to distinguish. Because the child has to decide if do you have abdominal pain. And you know, they are young. You say, does that hurt? Yes, it hurts. Well, how bad is it? It's very hurt, you know.

So my test is not really literally comfort. I say well, can you jump? If they can jump, it's not a peritonitis sign. Well, don't tell surgeon I said that. But it's in the clinic, you say, OK, can you jump. Make it fun. If they jump, walking around, not holding it, then that abdominal pain is likely from bursitis.

But if they say, well it hurts, and they have a fever, don't wait. Send them to the emergency room. They need to be [INAUDIBLE] need to be put on antibiotics quickly. And the prevention, of course, make sure they are immunized.

Another potential actual serious complication is thromboembulism. And this is because of several reasons. One is you've got hemoconcentration, because you are losing the water. And you are losing some low molecular weight anti-coagulant. And because the liver, it tries to make up for the loss in urinary protein, but unfortunately liver does not know what kind of protein the kidneys are losing. So it just makes up all sorts of proteins.

So in fact, in nephrotic symdrome, patients are losing low molecular weight, not the high molecular weigh pro-coagulant. There's all kind of factors there. So for this reason you have an increased level of those coagulation proteins. Plus you have the reduced blood flow.

So it's like 1 plus 1 plus 1 give you 6. And so this is very serious. Because they can die over this. And this is one of the complications.

Now, we don't even know how often that happens. I show you the instance, that's old data. But recently there is a group from Europe. I think they've got a lot of money. You know they use the CAT scan on every children with the nephrotic syndrome. You see, you won't have the kind of-- you won't pass the IRB if you want to do that test. They claim that is from everything, it is 40-50%. But a lot of them are not symptomatic.

And mostly they're venous thrombosis. But of course, arterial thrombi can happen. Usually it's on the lower leg. That's mostly because the edema happens mostly on the lower extremity because of gravity. So that adds more problem to it. And it's difficult for blood to pump up, and there can be pain and swelling.

So you had to go high or low, always think about this. Is somewhere in nephrotic syndrome you start thinking, is this is a clot there?

And the last one, the cardiovascular, of course, you have elevated lipids, hypertension. We saw some of the immunosuppression, per se, causing hyperlipidemia, too lipids in the blood.

So again, if you see a patient who with facial edema, the first thing you say. Well, where does the edema come from? Is that from kidney? Then you check the urine protein. You check the serum albumin.

Then the next thing you see, if the child looks good, you start on your mind, and say well, how bad is the edema. Is the edema causing trouble? And are there clots there? Are there cardiovascular problems? Are there infections? Are there endocrine problems? Are there kidney problems?

So these are the main six categories of complication you have to keep in mind. And every child you encounter, you have to go through that, so they don't miss them.

So you do the urine protein first, usually in clinic, in the office you do the dip sticks. But I want to warn you. The albumin-- the office dip sticks only detect albumin. A lot of reports tell you protein, but don't buy it. It's albumin. Albumin is only 15% of urinary protein. So very often I'd see a patient who has normal dipsticks, and you do protein creatinine ratio, that can be high. So if you suspect that, do spot urine protein-creatinine ratios. Or you can do 24 hours.

Then the next thing is that you did the CMP and found out the albumin is low. Then you start going through your mind, what is a potential complication. Of course, you should do your ABCs first. If the patient has breathing issues, you see well, check pulse asymmetry, those kind of things.

In the meantime, the workup first, to exclude the secondary causes. These are the general panel I do. But of course, you have to look for more, other [INAUDIBLE] findings and other things, try to exclude them.

Now let's say, I won't go into the secondary cause of nephrotic syndrome, because there's a long list. But I want to get into idiopathy. That mean that we don't know what caused it. Because family, that's the first question the family asks you, why my child has it.

Now I show you this data. It's the International Society of Kidney Disease Consortium, 1978. That's the data. It tells you a child presenting with idiopathic nephrotic syndrome. What is the underlying pathological finding?

The first one is the minimal change disease, almost 80%. And then for ages between 2 and 6, presented before 6 years old, 79% has the minimum change disease. These are the data showing that. And what I didn't-- I forgot to put it there, is 80% of minimum change disease that is idiopathic is responds to steroids.

So the chart, according to the data, for children less than 6 years old, there is 0.80 times 80% chance that will be 64% chance that it will be minimum change disease. And this is the reason that [INAUDIBLE] are rational. Therefore child within that age range, we empirically use steroids. If they respond to it, it's consistent with it. Of course, it does not confirm it.

And then you sit tight, and see how they do. Because one third will get into remission by itself later on. One third will consistently require steroids intermittently. One third will not respond to it. But this is the data they talk about 6 years old. But now we are using 1 and 1/2 years to 10 or 12 years old.

The reason because these data are old. So as the year goes by, each one has a different encounter, so slowly, slowly. That it's a consensus is 1 and 1/2 years and between 10 or 12 years, or even among nephrologists who have the argument-- I was one of the members that come up with the guideline of the AAP guideline for nephrotic syndrome in 2009. You don't want to know. We have a lot of discussion.

I say, well, you know what I think. We use 10 years old. Anyone older than 10 years old, you don't even ask. You do biopsy. Someone said, no, no. We should do 12 years. Well, what's your data? Well, what's your data?

So just to let you know, so we still don't know a lot. Because of that, then-- so just to let you know, it's kind of sad. Or I should not say, embarrassed for nephrologists that the management I'm going to show you later on is dependent on the data in the '60s, '70s.

Now so let's say what's the management. Of course, you deal with the symptoms, edema, infections, thromboembolism, nutrition, and ACE inhibitors usually can reduce the protein loss. But you have to be very careful with those with the kidney dysfunction.

This is the diagram, still kind of most centers use it. If a child between 1 and 1/2 years to 10-- I use 10 years old. Because I seem to see more of patients not minimum change disease after 10 years old.

And the therapy gives 60 milligrams per meter squared per day, or 2 per kilo per day. We gives this for six weeks, at least six weeks. Because studies showing that less than six weeks have more chance of relapse.

Then you see how they respond. If they are sensitive to it, then you kind of watch it. They can respond to it, but then it keeps coming back. Or you can not even taper them off steroids. In this case, you need to find a steroid sparing agent. That's where the biopsy comes.

Or they are resistant to it. You say, well what other medicine can we use? That's where biopsy comes. Then depending on what the biopsy shows, then you choose what the alternate agents are.

So let me go back to here, just saying that well, what we just show you, depends on the data in the '60s-70s. So we feel that there's a need to come up with another registry. Because we know that in the past 20 years that we have more cases of FFGS or membrane than we're used to. Because of changes in the environment.

So, some of us decided together. Let's re-look at what are we dealing with, with child nephrotic syndrome now. And you still do the kind of observational prospective registry. This is a NIH sponsor. And these are the participating centers. We were one of them.

And it's basically very simple. We just started, enroll the patient within 30 days of treatment. And then we do what we are supposed to do. We don't do intervention. And see are we seeing different type of patients than 20-30 years ago.

So I want to give you a very brief, very shortly that these are alternate medications. It looks confusing. You say, well what are they? But actually, don't ask me details of this. But I just show you.

We know the immune response start with antigen presents itself, usually as a macrophage. That's on the left-hand side there. Then the macrophage presents antigen to the T-cells. Then the different type T-cell, mainly CD4 and CD8, they start to amplify.

One of the cytokines that's inducing the amplification of CD4 and CD8s is Interleukin-1. And you can see, this here, that's where the steroid [INAUDIBLE].

Then the CD4 and CD8, they can produce Interleukin-2. You see that in the middle. They can interact with each other, amplify the loop. That's where the calcineurin inhibitor like Prograf and cyclosporine work.

Then on top of the roof, you see there in the middle that the CD4 cell and helper cell they can activate B-cell making immunoglobulin. And this part is broken by a [INAUDIBLE]

And then at the end, the B-active macrophage had to go, so you need a complement. And there's a lot of protein there. You can do plasma, for instance, to remove them. So that's already there. So that's what we use.

And as a matter of fact, if you use the steroids, Prograf and CellCept, those are standard triple immunosuppression after doing a renal transplant. So basically what we do is start a steroid first. It doesn't work. Let's choose Prograf. It doesn't work. How about CellCept? Not so good. Well, how about combining them? Yeah. This is still what we're doing now. Because a lot of times we don't know the etiology.

Now prednisone we have the list of complications. I will not read it. For I think many of you are familiar with this. And Prograf, Tacrolimus/Cyclosporine, most commonly they're causing the hair loss. They have the hypertensions, headache, and electrolyte loss.

Mycophenolate most of times the main side effect is GI. A lot of patient have to stop it because of GI issue. Because it reduces immunoglobulin production, and so it causes bacteria and fever sometimes.

So that's where I'm going to stop here. Because after this stage, we do biopsy, then we start to see which one we want to choose. But again, when you see a child with swelling, you say now, where is this swelling come from. Is that from the kidney? If it's a kidney, then you should see a lot of protein in the urine. You should see a low albumin.

And then you start thinking about complications. I usually do it from head to toe. Right? In the head, well, they can have ICP, because the fluid shifts. They have meningitis. They might have an eye issue. And do they have a thyroid issue or not? Do they have heart issue, like pericardial effusion? Or do they have a lung issue? They don't breathe well [INAUDIBLE], or they have a decreased oxygen situation. There could be infections. There could be a clot. It could be too much fluid.

And they go the list all the way up to the bottom. That's my habit. I mean you can do any way you want to. But that's usually when you see a child you suspect with nephrotic syndrome. That's what I look at, and it makes it a lot easier. Because you have a systemic way.

Again, assess complications. Then you understand that the kidneys is a trouble-maker, losing protein. So you have fluid shift to the [INAUDIBLE]. And from there, it initiates all kinds of complications.

And to deal with it, very simple. Well, how do we deal with the edema? No problem. I give albumin, right? Increase oncotic pressure quickly. The water shifts back. Make good urine. The swelling gets better. And the parents look at you, and say, wow. Like magic.