

[MUSIC PLAYING]

JAMIE So right now, I feel like I have to condense about 10 hours of data into 40 minutes. And I will not do that by speaking incredibly rapidly. I'm going to try to give you some pointers about this particular topic that I think that you'll find useful.

So the first thing I'd like to tell you is I have no disclosures. I'm an academic and that means I don't make very much money, compared to our private practice colleagues. And then none of us will be making more money as time goes on. So one of the things, or three of the things, that I want you to get out of this talk are to be able to list some consequences of chronic kidney disease that you can have an impact on, to recognize when to refer to nephrology, and to some basic maneuvers that will help you in treating the consequences of chronic kidney disease.

So one of the things to point out to you is that, as you already know, this is something that you're going to be seeing a lot of. And that the 2013 estimate was there were about 20 million Americans that were adults that had chronic kidney disease, which roughly translates into about one out of every adult American. This figure varies a little bit, it has been as high as 26 million. But needless to say, as you all know, you're going to see a lot of chronic kidney disease.

In 2002, KDOQI described the stages of chronic kidney disease. Stage 1 would be structural damage, those would be patients that had polycystic kidney disease, but had preserved function. Stage 2 would be someone that had a little bit of reduction in renal function, perhaps had protein in their urine. Stage 3 is moderate decreases, and generally it's broken into two groups. 45 to 60 is stage 3A, and stage 3B-- which is what I'm going to be primarily talking about-- is 30 to 45 mL/minute of GFR.

Severe renal dysfunction is, and I'll say this and reiterate this, would be a GFR that is on the order of about 15 to 29. And stage 5 is when we're considering people for transplantation and initiation of dialysis. One of the things about this is, why do we have a cut off of less than 60? And if you look at this slide, one of the things that will become evident, this is age-standardized rate of death, on the y-axis. And on the x-axis, you see that there is a nice big jump in mortality, once you go below a stage 3A to stage 3B. And that's one of the reasons why I want all of us to pay attention to this.

So that's something that I think is why this talk is geared towards that. One of the other things that I want you to notice is, this is the prevalence in adults over the age of 30. This is kidney disease stage 1. And you can see the blue line is the current number of folks with it. 2020 it goes up a little bit, 2030 it goes down. This is primarily due to the introduction of ACE inhibitors, which have been a godsend to us in the renal field.

What you'll notice is they already have stage 2, it increases. And if you have stage 3A, it really increases, but then look at this. Look what happens at stage 3B. And the reason that this happens in stage 3B is because of coronary artery disease, which I'm not going to talk about today, because I really consider this to be one of our really gold standards of something that we have to be all aware of and treating. But there is a huge mortality rate that occurs in stage 3As, and this is something that we all have to pay attention to.

If you look at kidney disease, I found in my medical school class, which I just finished teaching. One of my students asked me, he said, "Well, jeez, you know, you put him on dialysis, and they just live, right?" Well, no, they don't. And one of the things, if I gave you a multiple choice test and said which would you rather have, lung cancer, kidney failure, or colorectal cancer? The right answer would be colorectal cancer, because you would live longer than if you have end stage renal disease and you're on dialysis.

The average mortality rate, per year, when you're on dialysis is about 20% per year. And that's one of the reasons why it is extremely important for us, as practitioners, to really try to keep people from progressing. So just as I already gave it away, what is the most common cause of death in chronic kidney disease? It's definitely cardiovascular disease.

And therefore, as a basic underlying tenet, in my talk today, coronary artery disease prevention is absolutely critical. The areas that I am going to cover today-- and this is going to be one of the most controversial-- is hypertension, anemia, secondary hyperparathyroidism, which is changing. And when we approach and treat this. Water, sodium, and potassium abnormalities, and some of the things that we can do early on, and then acid-base disturbances.

And I'm going to present some data that I was taught 30 years ago. But which, finally, they have now-- yeah, Dr. Stars is smiling at me, he taught me some of this stuff. But he was a child prodigy, he started being a doctor when he was 10.

[LAUGHTER]

And we'll talk a little bit about acid-base disturbances. So primary hypertension, which is the most common causes is of unknown etiology, there are 30 candidate genes that have been identified. We still can't identify a single unifying hypothesis for primary hypertension. But the one that I want us to focus on today is secondary hypertension, which is the chronic kidney disease group, is primarily due to salt and water retention. Or the inability to get rid of salt and water loads appropriately.

And one of the things I want you to remember is that chronic kidney disease is the major cause of secondary hypertension. So current goals of care, I'm sure all of you have pondered the current controversy between the Joint National Commission, JNC 8, which was released in 2014. And then immediately followed up by one of the authors of the JNC study with the SPRINT trial, the Systolic Blood Pressure Intervention Trial.

And no matter what either of these studies say, the take home point from this part of the talk is that hypertension control is absolutely essential, in order to slow the progression of chronic kidney disease. An outstanding example of that is the control of blood pressure with ACEs and ARBs and diabetes. If we were going along at the current rate, the incidence of diabetic nephropathy now would be almost twice of what it is currently. But because of the introduction of the ACE and ARB therapy, that's dramatically slowed.

Incidence, still though, keeps going up, primarily because the heart doctors are doing a better job of keeping people alive. And secondarily, we're doing better in terms of blood pressure control overall. So they're living longer so that they can develop diabetic nephropathy, obesity and congestive heart failure. I apologize for this slide, which, this one of the things I hate as a teacher. You never should have something that this is complicated, but let me walk you through it step-by-step.

So a patient walks into your office, and you check their blood pressure, and you find out that it's high. So you have an adult greater than 18 years old of age with hypertension. What do you do about that patient? The very first thing you do with that patient is say, I want you to take power of your blood pressure, and I want you to get a home blood pressure monitor and I want you to take your blood pressure at home. This is now the current standard of care recommended by the 2013 guidelines from the American Heart Association.

If the patient's insurance will not pay for a 24-hour ambulatory monitor, which is just as important, then teach them to go to the local pharmacy and get a blood pressure cuff and keep a blood pressure log. If they verify that they have high blood pressure at home, then the next thing that you're going to do is going to be lifestyle modifications. And that's going to be DASH diet.

There are increasing amount of evidence that show that a high-potassium diet, with monitoring of the potassium, actually has a diuretic effect on one of the transport segments in the kidney. And may be one of the reasons why a high-potassium diet actually will help control blood pressure. Our current diet has gone from being low in sodium and high in potassium to low in potassium and high in sodium. And it's one of the, major causes I think at this time, for the increase in hypertension.

So if you get them to exercise, you get them to control their weight, you control their cholesterol, they've done everything right and they're still hypertensive, usually you give them about a three-month period. Then what you have to do is you have to go and start to generalize them into general groups.

You have the general population with no diabetes or CKD, and then you have the group with diabetes or CKD. And one of the nice things about the JNC 8 is that it really has tried to simplify our goals for this. So it's not hard to remember.

And what you'll see, is that once you stratify into these groups, you have 150 over 90 as being the goal for patients over the age of 60. And then every other goal is 140 over 90 or less for people younger than 60. People that have no diabetes, or they have diabetes, but no chronic kidney disease. Or they have both CKD with or without.

The next thing that they do is they give us a group of medications, pretty simple to remember. For diabetes, ACEs or ARBs, because they have proven to be the most effective in preventing the progression of renal disease. And then for African Americans, thiazides or calcium channel blockers. And then for European Americans, and these are really not applicable to Asian Americans. These studies have not been done in regard to that. But what you should do is to do a thiazide, or an ARB or ARB, or calcium channel blocker.

One of the things that you'll notice that is really obvious from this is, where the beta blockers? Beta blockers, about 20 years ago, were a mainstay for this. And what they've found is that there's a 14% to 26% increase in the number of strokes in association with beta blockade in a hypertensive population. So now what we're recommending is that you should only use beta blockade when you have strong coronary artery disease indications.

So I like the JNC 8, it was a very well done study, multiple analyzes, a lot of different subgroups in it. And it's one of the things that I keep in the back of my head. Now they came out later on with the SPRINT trial, and the SPRINT trial is really hitting the ACCORD trial. The ACCORD trial was 45,000 patients that stratified them into two groups, a standard blood pressure group and an intensive blood pressure group. The major difference between ACCORD and SPRINT is that SPRINT did not include diabetics.

If you look at this, they were successful in their goal. Standard treatment put the patient at about 135 systolic, and the intensive treatment was down around 121. And what they found, in looking at this particular group, their outcomes were looking primarily at coronary artery disease. And what they found was that if you systematically lowered the blood pressure to 132 or less systolic, that they had a significant decrease in the amount of coronary artery disease events.

Now the article reports a 43% decline in the coronary artery disease incidence. What does that mean? It means that the coronary artery disease events went from 2.16%, in the standard group, down to one 1.65%, in the study group. And when you present it as a 43% reduction, that sounds great, let's buy stock in the companies, right? Well, no, in this particular case, it's a very small change.

And the other thing that they noticed, in the intensive care group, that there was a significant increase in the number of, basically, adverse events in the intensive treatment group. So one of the things that we all know is you never get something for nothing in what we do. And you can do intensive therapy, and it can cause problems, as well, even though it may be of benefit.

But all-cause mortality was lower in this group. So this is what I want you to take home from this, OK, here's Charlton Heston, very nicely done hair, really coming down off the mountain. You all know that there were 15 commandments, right, but he dropped five of them on the way down.

And the thing that I want you to remember is goals are guidelines. They are not commandments. It's not something where we're going to go and we're going to push this so that we get our patients down, and they're falling down and breaking their hips, and doing things like that.

And the other thing that is not consistently mentioned is, let's go back to the diabetes trial, where they first used captopril. A 50% reduction in the rate of progression of diabetic nephropathy with captopril being given two or three times a day. Do you know what the blood pressure lowering was in that study? The average blood pressure lowering that caused a 50% decrease in the rate of progression of diabetic nephropathy was three millimeters of mercury. So what I want you to remember is you get a lot for a little in this particular field.

So these are Jamie's rules. Adjust the therapy according to the individual patient. Use proteinuria as a goal, try to keep the protein excretion less than 500 milligrams a day. And then finally, push the therapy and get the lowest blood pressure, with the fewest medications and the smallest number of side effects.

And the goal police are not going to come into your office and arrest you because all of your patients don't have a blood pressure of 120. I assure you that they won't. That's the blood pressure thing, which I actually considered to be probably the most important part of my talk today. Next part is CKD stage 3B anemia. And the etiology of this is really multi-factorial.

And if you look at the variety of different things that happen, erythropoietin production really starts to go down very, very early in chronic kidney disease. Patients also have an inability to absorb iron because, believe it or not, your stomach doesn't excrete as much acid whenever you have chronic kidney disease. So you can't change iron, that charge on iron, to the charge that's appropriate for it to be absorbed in to duodenum.

Your red cells don't last long in stage 4 or 5. Red cells may only last 60 days, instead of 120 days. And there's this clever little chemical that the liver makes called hepcidin, which levels go up. And in that particular case, when hepcidin levels go up, you decrease your gut iron absorption, and the macrophages, which are carrying the iron around, really can't talk to the liver cells and show them how much iron they're carrying. So it decreases macrophage-liver cross-talk.

This happens very, very early, and I remember an old study from the 1970s-- yes, I'm that old-- where the hemoglobin started to decrease very, very early, and they found out that it was a very linear correlation. So with serum creatinine levels of less than two, 45% of the patients already had hematocrits that were less than 36%. And that even with creatinine clearances in stage 2 chronic kidney disease, you had significant differences and decreases in hemoglobin.

The NHANES study three, one of the older NHANES trials-- this is from around 2002-- basically showed that 800,000 patients with CKD at that time had a hemoglobin of less than 11 grams per deciliter. So the answer to this is to monitor, monitor, monitor. And you have to follow the ferritin, iron and transferrin.

The goal is to keep the ferritin around 130. And one of the things to remember is that ferritin is acute phase reactant, so if your patient's in the hospital and they have pneumonia, the ferritin it might be 1,000. So you can't really monitor ferritin whenever someone's sick, it has to be a steady state sort of thing.

The second goal is to maintain the percent transferrin saturation greater than 20%. Should you normalize your patients? Should you try to get them up to hemoglobin or hematocrits that are normal? And the answer to that is that you should not, because if you try to normalize blood counts in someone with chronic kidney disease, you increase their cardiovascular mortality.

So one of the things I like to say, normal is for normal, but normal is not normal for people that have chronic diseases. You have to be very, very careful with this. As in type 2 diabetes, if you try to take the hemoglobin A1c-- and Fred's going to probably throw something at me now-- but if you try to take the hemoglobin A1c down below seven, you do have a demonstrable increase in coronary artery disease events. That data hasn't yet shown for type 1s.

So what you can try, is you can try oral supplementation, but if you fall below the goals, you probably should team up with the hematologist. Give them IV iron.

[MUSIC PLAYING]

Excuse me, folks. It's from Cooperstown, New York. One of the things to do is--

AUDIENCE: [INAUDIBLE]

JAMIE JOHNSTON: It was my days as a shortstop for the Pirates. Yeah, and if you believe that, I have a couple of bridges downtown I can sell you.

You really don't start EPO therapy until they're under hemoglobin of about nine, and this is really something that should be done by a nephrologist, or by hematologist. Please, please, please, don't measure EPO levels in patients with chronic kidney disease. It's a waste of money, it's very expensive. If they have chronic kidney disease, the EPO concentrations start falling in stage 2. They are going to be low, it's not going to help you any.

So let's talk a little bit about calcium phosphate and that particular happenstance. So I think you all know that as renal failure progresses, that the production of 1,25 vitamin D in the kidney falls. And with that, calcium absorption from the gut falls, and also because of the decreased renal mass, calcium reabsorption will fall, and that will cause a secondary increase in parathyroid hormone.

Parathyroid hormone in large concentrations is a bad actor. The hyperplasia in and of itself-- we'll go into that in the next slide-- but phosphate excretion will also decrease, because it continues to be reabsorbed from the gut. Primarily because 30% of phosphate absorption in the gut is independent of vitamin D therapy. And the serum phosphate level will rise because the kidney is unable to excrete phosphate the way that it normally does.

The consequences of this are that the parathyroid hormone gets very vexed with the kidney, and it decides that what it's going to do is it's going to stimulate the osteoclast in the bone, and it's going to mine calcium out of the bone. So you can get renal osteodystrophy, which is basically a type of osteopenia. And you can get osteitis fibrosa cystica, which really is, basically, rickets, in a renal disease patient.

There's an increased fracture risk that goes along with this. This can cause a huge amount of morbidity. One of the other things that has come out of this is that you can have accelerated atherosclerosis. And one of the things that they've been able to show is that the atherosclerosis is related to bone deposition outside of the bones. You start to have bone formation with osteoblast and osteoclast in the blood vessels.

Another one, a little new kid on the block, is we finally figured out how the bones talk to the other organs. And that's fibroblast growth factor 23. Yes, there are 22 that have come before it. But 23 is the one that we're concerned about.

If you look at fibroblast growth factor 23, its primary effect is to decrease phosphate reabsorption, and to keep the phosphate levels normal. Unfortunately, what it does is it increases coronary artery disease mortality. And that effect is evident in stage 2 CKD with GFRs that are on the order of about 70 mL/minute.

This has resulted in a huge controversy within the nephrology field, about when do we start binder therapy on these folks? Do we start binder therapy whenever the FGF23 is keeping the phosphate at around four-- which would be a desirable value-- or do we give them calcium phosphate binders, when now it's been shown that the calcium phosphate binders may contribute to atherosclerosis? Do we get them phosphate binders, like sevelamer or Fosrenol, that actually are quite expensive and many patients can't afford?

This is really, really out there. My own personal belief, This goes under the little asterisks next to me of an editorial comment, I really think that we should be treating them, you should be phosphate restricting them at this point. Even as early as stage 2, they should be having dietary interventions about this. And really only use phosphate binders whenever you can't get good control. But you really have to try to keep FGF23 down.

This shows what you have to do when you have renal failure, in order to sustain calcium at normal levels. And one of the things that you'll notice, is that the parathyroid hormone is already starting to go up here in the stage 2 chronic kidney disease, and gets up to very high values. The current guidelines are shown in this table. And these are from the Kidney Disease Outcomes Quality Initiative, which are really our Bible, in renal medicine, about how we treat these folks.

In stage 3, which is the group that I'm talking about for my colleagues in the audience, you try to keep the phosphate between 2.7 and 4.6 And you'll notice that the parathyroid hormone is about 35 to 70. This is right at the upper limit of normal. Then if you go into stage 4, you'll notice that it goes up. And if you go into stage 3, it's almost four times normal.

The reason that you need this high level of a parathyroid hormone is so that you can have normal bone remodeling. If you don't have a high PTH level, you're going to get adynamic bone disease. Your bone, which is constantly remodeling as we walk around during the day, will not do that and you'll end up with fractures, as well.

So this is a delicate balance between the phosphate concentrations, the calcium, and the parathyroid hormone. And in my patients. It's not uncommon at all to change their phosphate and calcium therapy. Usually about 60% of my patients each year have some sort of modulation in their calcium and phosphate therapy. It takes a lot of monitoring and a lot of attention to detail.

So what we can do to treat this is we can increase the amount of calcium reabsorption from the gut, by using 1,25 vitamin D analogues. And remember that you can supplement 25 vitamin D, either the D2 or the D3, form but you needed intact kidney, in order to add that one hydroxyl group to make it active, in order to absorb calcium. So in this particular case, you're going to give active vitamin D.

You can use calciumimetics, which react with the calcium sensing receptor on the parathyroid glands, and will decrease parathyroid hormone. Or you can go the surgical route of doing total and subtotal parathyroidectomy. To In my 30 years of practicing as a nephrologist, as I have seen this paradigm change four times. It's not done yet, It's probably going to continue to change.

You can control phosphate retention, you can do dietary restriction of phosphorus, which is extraordinarily difficult, because you want these patients also to be adequately nourished. And protein bearing foods are high in phosphorus. As a matter of fact, most foods are high in phosphorus. So this is going to be very, very difficult. And if you can't control it with, diet you're going to probably have to go with some sort of phosphate binder.

You really want to try to decrease daily intake to about 800 to 1,000 milligrams a day. The daily intake of phosphorus in an American diet is probably between 1,500 and 2,000. It's a very restricted diet, but it does help decrease parathyroid hormone synthesis, and it will do that independently of serum calcium and calcitriol levels.

And really, as chronic kidney disease gets worse, you're going to have to use a phosphate binder in these folks. I expect that for most of you, that if you follow the current guidelines, and are referring to nephrology, the nephrologist is going to be the one that's going to be starting the phosphate binder, and not necessarily you. I would request that my colleagues in the audience go after diet control, as being probably the most important way of doing this.

Sodium, water, and potassium-- here I feel like the rabbi Hillel, being talked to by the skeptic, and asking me to explain everything that's important about Judaism, while I stand on one foot. Which, for those of you that don't know that parable, it is, in this one thing be true, treat others as they would treat you and all the rest is commentary. So I can't do that for nephrology, because I am not as smart as Rabbi Hillel, and I am Presbyterian, so.

[LAUGHTER]

What can I tell you? The two most common disorders, usually on the order of about 25% incidence in both populations, are low serum sodium concentrations and high serum potassium concentrations. And this is straightforward, you don't have enough kidney mass to excrete the extra water, and you don't have enough kidney mass to excrete the extra potassium. So you're going to retain water and potassium.

One of the things that my patients come in and tell me all the time is, I've been told by the Pittsburgh Post-Gazette that I should drink 120 ounces of water a day. And that really is an urban myth. Drinking a lot of water is not good for your kidneys, unless you know you want to say that-- it's just a completely unnecessary association that peeing a lot means that your kidneys are working well.

There are only two situations where you should really drink a lot of water, and that is and women that have recurrent urinary tract infections. And the second one is when you have people that form a lot of stones. Other than that drinking a lot of water just is making the toilet paper company and your water company richer.

So the advice that we give to folks is that if they don't have recurrent urinary tract infections, and they don't have kidney stones, that they should drink enough fluid to quench your thirst. You have a nice little center in your brain that does that very well. And if you do that, you'll be able really to eliminate the need to push water.

As far as edema goes, which is a state of total body salt and water overload, with too much salt and water on board, you should limit the sodium intake. Now people can get crazy with this, and if they do it abruptly, and they have chronic kidney disease, they will get into trouble. Because taking a patient with chronic kidney disease and saying, OK, you're going to have to go on a two gram sodium diet, and I want you to do this right away.

And the patient's all scared because they think they're going to die of a stroke or a heart attack. Well, when you do that to a damaged kidney, it's the equivalent of taking a coal barge on the Monongahela River, and trying to do a complete turnaround in 15 seconds. It's not going to happen. That kidney will continue to waste sodium, and you'll end up with a patient that has volume depletion and hypotension.

What you should really do is to tell the patient to ease into this, and the easy advice is to tell them is to get the salt shaker off the table. Get the salt shaker off the stove, and have a mind about what you're eating, and then how high in sodium so many processed foods are. And I really tell patients to try to buy fresh. One of the difficulties you run into that is it's expensive, and many of our patients live in food deserts. So you have to try to do what you can with this, but no added salt is really practical advice.

Potassium restriction is about 60 milliequivalents, or about 2,300 milligrams a day, this has to be done with, basically, food sheets that tell you what high content potassium foods are. And you have to be very, very careful about monitoring the potassium level in these folks, so you start them on a angiotensin converting enzyme inhibitor, an ARB. You really have to check the blood work within a week, because their potassium might go up, and you also want to check what the effect on their renal function was.

The other thing is you can put them on a nice thiazide diuretic and they come in a week, and they can't move and they have constipation, because now their potassium is so low that their muscles no longer work. So this is really something that has to be done in close conjunction with the dietitian. So that if we follow Dr. Romito's advice, and go and go in together, on joint dietitians together, we can actually work on doing this. the dietary management is very important.

Getting close to the end. Stage 3 and acid-base, the kidney at this particular point can't regenerate or reclaim bicarbonate. And the consequences of this include the gradual muscle weakness and bone damage that happens from hydrogen ion accumulation. Your bones buffer hydrogen, and one of the things that causes the renal disease, or the renal bone disease, is buffering of bones by hydrogen.

The other thing is you get progressively weaker because there's a direct inhibition of muscle formation by acidity in the blood. There's also an association with increased mortality. So again, back when I was working with Dr. Siegel, and Dr. Bruns, and Dr. Frayley, and Dr. Adler, I was always told, keep the bicarb level between 24 and 26. And I'd say where's the data? And they would say, believe me. And I said, OK, I'm just your fellow, so I'll believe you.

Well, now there's data on it, and what the data show is that if you maintain the bicarb level between 23 and 32, you have the lowest rate of mortality, but if you let that bicarb rate go below 23, your mortality increases. And contrary wise, too much of a good thing, increasing the bicarb up to 32, also has a mortality effect. So this is very, very easy to do, bicarb supplements are quite easy.

You replace them, you try to keep them between 24 and 26. And then I'll ask you how many milliequivalents of bicarb are there in a 650 milligram tablet? 7.7 milliequivalents. For the chemists in the room, they already calculated the bicarb as a molecular weight of 84 milligrams per millimole.

And just for the historians in the room, 650 milligrams, why is that number-- why do we use that number? Because that's 20 grains. So we're still having these echoes from the 17th century about the way that we measure things.

So when do you keep calm and call the nephrologist? Well, you can call me anytime, I love talking to my colleagues. And one of the things that we've done at Presby, we have instituted an e-consult service. So that if you have someone that you're concerned about, and you just want to talk to us about it, you can use the e-consult service, which is available through Epic. Please use that, we're happy to help.

But if the GFR gets below 30, you really should give us a call. And the role of the internist in this is really, really important, because based on the total number of chronic kidney disease patients now, and the number of nephrologists-- there are only 7,000 of us. OK, if we took care of all the chronic kidney disease patients we would be seeing 4,000 patients per year. And the only one in the room that I know that can see that many patients is Dr. Bernstein, so.

[LAUGHTER]

That's a slow day for him, and with that, I'd like to say thank you, and I'd be happy to answer any questions.

[APPLAUSE]